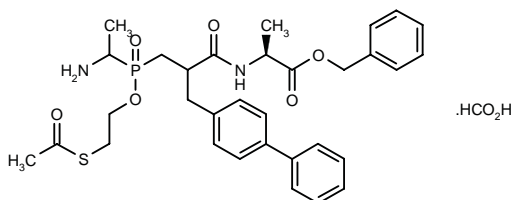


ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

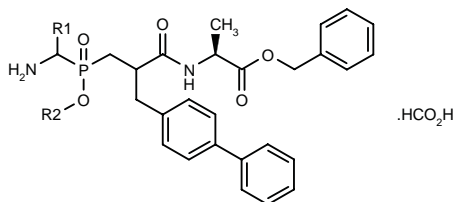
282306

N-[3-[[2-(Acetylsulfanyl)ethoxy](1-aminoethyl)phosphoryl]-2-(biphenyl-4-ylmethyl)propionyl]-L-alanine benzyl ester formate



C32 H39 N2 O6 P S . C H2 O2; Mol wt: 656.7329

ACTION – Dual aminopeptidase N (membrane alanine aminopeptidase) and neutral endopeptidase inhibitor that inhibits the degradation of enkephalin and presents certain properties of morphine-like substances, particularly analgesic effects, beneficial behavioral effects (antidepressant, sedative, anxiolytic, disinhibitory and cognition-enhancing effects), as well as peripheral effects (antidiarrheal, antitussive, hypotensive, antiinflammatory effects). In contrast, it is not associated with the undesirable effects of morphine-like compounds. Compound is reported to be active following i.v., s.c. or p.o. administration. Other exemplified (α -aminophosphino)peptide derivatives include the following:



Compound	R1	R2	Formula
282307	Me	CH ₂ CH(Me)CH ₂ OAc	C ₃₄ H ₄₃ N ₂ O ₇ P·CH ₂ O ₂
282308	Ph	CH ₂ CH ₂ SAc	C ₃₇ H ₄₁ N ₂ O ₆ PS·CH ₂ O ₂
282309	Ph	CH(i-Pr)OAc	C ₃₈ H ₄₆ N ₂ O ₇ P·CH ₂ O ₂

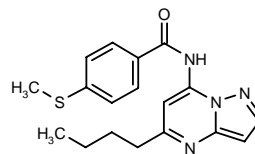
SOURCE – INSERM, Paris Cedex (FR).

REFERENCES

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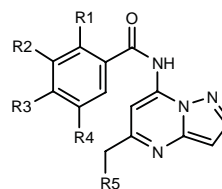
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N-(5-Butylpyrazolo[1,5-*a*]pyrimidin-7-yl)-4-(methylsulfanyl)benzamide

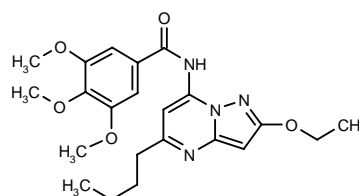


C18 H20 N4 O S; Mol wt: 340.4490

ACTION – Analgesic agent, a nitric oxide synthase (NOS) inhibitor representative of a series of pyrazolo[1,5-*a*]pyrimidine derivatives, wherein the following are also included:



Compound	R1	R2=R4	R3	R5	Formula
282929	Cl	H	Cl	CH ₂ Ph	C ₂₁ H ₁₆ Cl ₂ N ₄ O
282930	3,4,5-(MeO)3- -PhCONH	H	H	Pr	C ₂₇ H ₂₉ N ₅ O ₅
282932	H	H	SO ₂ Ph	Pr	C ₂₃ H ₂₂ N ₄ O ₃ S
282933	Cl	H	Cl	OCH ₂ CF ₃	C ₁₆ H ₁₁ Cl ₂ F ₃ N ₄ O ₂
282934	H	OMe	OMe	CH ₂ CF ₃	C ₁₉ H ₁₉ F ₃ N ₄ O ₄



282931: C22 H28 N4 O5

SOURCE – Otsuka.

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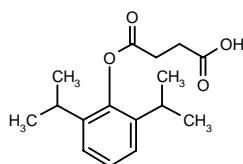
ANESTHETIC DRUGS

PROPOFOL HEMISUCCINATE

283159

Succinic acid 2,6-diisopropylphenyl monoester

4-(2,6-Diisopropylphenoxy)-4-oxobutyric acid



C16 H22 O4; Mol wt: 278.3458

ACTION – Water-soluble prodrug ester of propofol⁺ that is rapidly metabolized to propofol in the body and is nontoxic and more stable to oxidation than propofol. It was tested in several *in vitro* and *in vivo* assays and was found to protect rat cortical neurons and murine hippocampal HT-22 cells from glutamate toxicity, protect HT-22 cells from oxidative injury, reduce lesion volume in a rat model of mechanical spinal cord injury, and reduce the severity and/or time course of symptoms of experimental allergic encephalomyelitis (EAE), a rat model of multiple sclerosis. Potentially useful for treating inflammatory disorders such as arthritis, neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, Pick's disease, amyotrophic lateral sclerosis and multiple sclerosis, stroke, respiratory disorders, nausea and vomiting, epileptic or convulsive disorders and pruritus, as well as for inducing anesthesia.

SOURCE – Vyrex.

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*Drug Data Rep 1986, 08(11): 1017.

ADJUNCTS TO ANESTHESIA

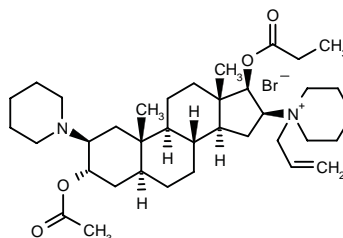
RAPACURONIUM BROMIDE

Prop INN

203872

1-[3 α -Acetoxy-2 β -(1-piperidinyl)-17 β -(propionyloxy)-5 α -androsta-16 β -yl]-1-allylpiperidinium bromide

Org-9487⁺



C37 H61 Br N2 O4; Mol wt: 677.8140

ACTION – Nondepolarizing neuromuscular blocking agent.

INDICATION – As an adjunct to general anesthesia to facilitate tracheal intubation and to provide skeletal relaxation during surgical procedures (inpatients and outpatients).

PRESENTATION – Sterile, nonpyrogenic, lyophilized cake in 5-ml and 10-ml vials, each containing 100 mg and 200 mg rapacuronium bromide base, respectively, for reconstitution for i.v. injection.

PROPRIETARY NAME – Raplon (US).

SOURCE – Organon.

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MONOGRAPH – Prous, J. et al. *Org-9487*. *Drugs Fut* 1994, 19(10): 0916.

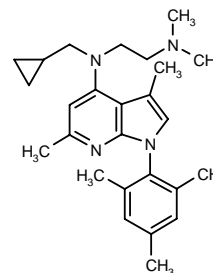
*Drug Data Rep 1994, 016(04): 0330.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

281941

N-(Cyclopropylmethyl)-*N*-[2-(dimethylamino)ethyl]-*N*-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1*H*-pyrrolo[2,3-*b*]-pyridin-4-yl]amine



C₂₆ H₃₆ N₄; Mol wt: 404.5984

ACTION – Agent for the treatment of stress-related disorders, depression, headache and anxiety, a selective corticotropin-releasing factor CRF₁ receptor antagonist. Other exemplified compounds from this series of pyrrolo[2,3-*b*]pyridine and pyrrolo[2,3-*d*]pyrimidine derivatives include the following:

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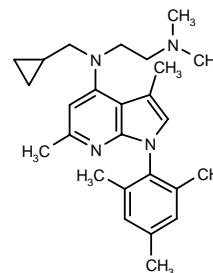
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PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

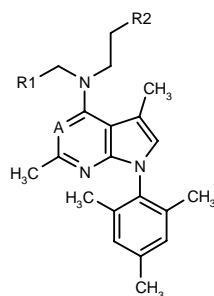
281941

N-(Cyclopropylmethyl)-*N*-[2-(dimethylamino)ethyl]-*N*-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1*H*-pyrrolo[2,3-*b*]-pyridin-4-yl]amine



C26 H36 N4; Mol wt: 404.5984

ACTION – Agent for the treatment of stress-related disorders, depression, headache and anxiety, a selective corticotropin-releasing factor CRF₁ receptor antagonist. Other exemplified compounds from this series of pyrrolo[2,3-*b*]pyridine and pyrrolo[2,3-*d*]pyrimidine derivatives include the following:



Compound	R1	R2	A	Formula
281942	cyclopropyl	NH2	CH	C ₂₄ H ₃₂ N ₄
281943	-CH ₂ NH-		CH	C ₂₂ H ₂₈ N ₄
281944	cyclopropyl	1-pyrrolidinyl	N	C ₂₇ H ₃₇ N ₅

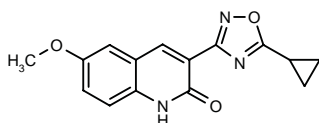
SOURCE – Neurogen.

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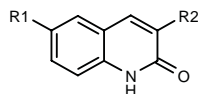
282885

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-6-methoxyquinolin-2(1H)-one



C₁₅ H₁₃ N₃ O₃; Mol wt: 283.2857

ACTION – Benzodiazepine agonist with high affinity for the benzodiazepine binding site on the GABA_A receptor, with an IC₅₀ value of 0.91 nM against [³H]-diazepam binding in crude synaptosome membrane preparations from rat brain. Other compounds from this series of 1,2,4-oxadiazolylquinolone derivatives include the following:



Compound	R1	R2	Formula
282886	OMe	3-Me-1,2,4-oxadiazol-5-yl	C ₁₃ H ₁₁ N ₃ O ₃
282887	Cl	3-Me-1,2,4-oxadiazol-5-yl	C ₁₂ H ₉ ClN ₃ O ₂
282888	OPr	3-Me-1,2,4-oxadiazol-5-yl	C ₁₅ H ₁₅ N ₃ O ₃
282889	OMe	3-Et-1,2,4-oxadiazol-5-yl	C ₁₄ H ₁₃ N ₃ O ₃
282890	Cl	3-Et-1,2,4-oxadiazol-5-yl	C ₁₃ H ₁₀ ClN ₃ O ₂
282891	H	5-cyclopropyl-1,2,4-oxadiazol-3-yl	C ₁₄ H ₁₁ N ₃ O ₂
282892	H	5-(2-furyl)-1,2,4-oxadiazol-3-yl	C ₁₅ H ₉ N ₃ O ₃

SOURCE – Dainippon Pharmaceutical.

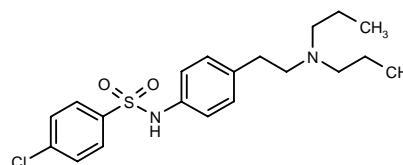
REFERENCES

- Ohno, K. et al. (Dainippon Pharmaceutical Co., Ltd.) *1,2,4-Oxadiazolylquinolone derivs*. JP 99279176.

ANTIPSYCHOTIC DRUGS

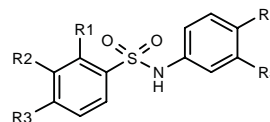
283181

4-Chloro-N-[4-[2-(dipropylamino)ethyl]phenyl]benzene-sulfonamide



C₂₀ H₂₇ Cl N₂ O₂ S; Mol wt: 394.9643

ACTION – Dopamine receptor ligand that exhibits good affinity for the D₃ receptor but only modest affinity for the dopamine D₂ receptor (K_i = 3.7 and 629 nM, respectively, in binding assays). Compound is therefore useful in the treatment of CNS disorders such as schizophrenia, Parkinson's disease, tardive dyskinesia, obsessive-compulsive disorder, depression and anxiety. Other specifically claimed phenylsulfonamide-phenylethylamines are:



Compound	R1	R2	R3	R4	R5	Formula
283183	Cl	H	Cl	CH ₂ CH ₂ NHPr	H	C ₁₇ H ₂₀ Cl ₂ N ₂ O ₂ S
283184	H	H	Cl	CH ₂ CH ₂ NHPr	H	C ₁₇ H ₂₁ ClN ₂ O ₂ S
283185	H	H	OCF ₃	CH ₂ CH ₂ NHPr	H	C ₁₈ H ₂₁ F ₃ N ₂ O ₃ S
283186	Cl	H	F	CH ₂ CH ₂ NHPr	H	C ₁₇ H ₂₀ ClFN ₂ O ₂ S
283187	H	H	Br	CH ₂ CH ₂ NHPr	H	C ₁₇ H ₂₁ BrN ₂ O ₂ S
283188	H	H	CF ₃	CH ₂ CH ₂ NHPr	H	C ₁₈ H ₂₁ F ₃ N ₂ O ₃ S
283189	F	H	H	H	CH ₂ CH ₂ NHPr	C ₁₇ H ₂₁ FN ₂ O ₂ S
283190	H	Cl	H	H	CH ₂ CH ₂ NHPr	C ₁₇ H ₂₁ ClN ₂ O ₂ S

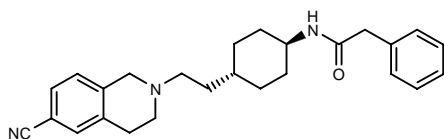
SOURCE – Pharmacia & Upjohn (Pharmacia).

REFERENCES

- Romero, A.G. and Leiby, J.A. (Pharmacia & Upjohn Co.) *Phenylsulfonamide-phenylethylamines useful as dopamine receptors*. WO 9958499.

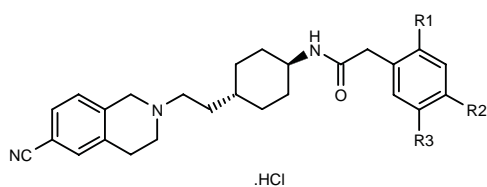
283376

trans-N-[4-[2-[6-Cyano-1,2,3,4-tetrahydroisoquinolin-2-yl]ethyl]cyclohexyl]-2-phenylacetamide



C₂₆ H₃₁ N₃ O; Mol wt: 401.5509

ACTION – Dopamine D₃ receptor modulator with higher affinity for D₃ receptors than for dopamine D₂ receptors, a profile suggested to be associated with useful antipsychotic activity but no significant extrapyramidal side effects. Other exemplified tetrahydroisoquinoline derivatives include the following:



Compound	R1	R2	R3	Formula
283377	H	F	H	C ₂₆ H ₃₁ ClFN ₃ O
283378	F	H	F	C ₂₆ H ₃₀ ClF ₂ N ₃ O

SOURCE – SmithKline Beecham.

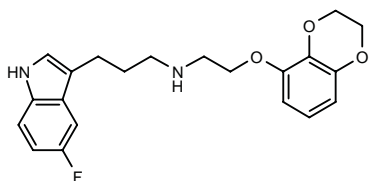
REFERENCES

- Vong, A.K.K. (SmithKline Beecham plc) *Tetrahydroisoquinolinolone derivs. as modulators of dopamine D₃ receptors*. WO 9959974.

TREATMENT FOR MOOD DISORDERS

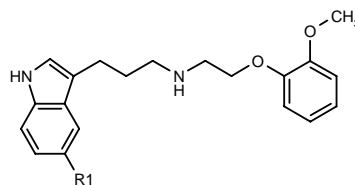
281694

N-[2-(2,3-Dihydro-1,4-benzodioxin-5-yloxy)ethyl]-N-[3-(5-fluoro-1H-indol-3-yl)propyl]amine



C₂₁ H₂₃ F N₂ O₃; Mol wt: 370.4217

ACTION – Agent for the treatment of depression and anxiety that is reported to act concomitantly at 5-HT_{1A} autoreceptors and the 5-HT transporter (K_i = 0.68 and 0.08 nM, respectively). Other exemplified compounds from this series of *N*-aryloxyethyl-indolyl-alkylamines include the following:



Compound	R1	Formula
281695	H	C ₂₀ H ₂₄ N ₂ O ₂
281696	F	C ₂₀ H ₂₃ FN ₂ O ₂

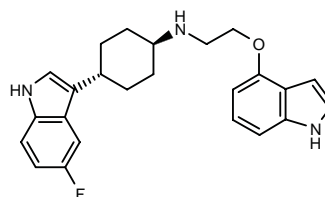
SOURCE – American Home Products.

REFERENCES

- Mewshaw, R.E. and Zhou, D. (American Home Products Corp.) *N-Aryloxyethyl-indolyl-alkylamines for the treatment of depression (5-HT_{1A} receptor active agents)*. WO 9951575.

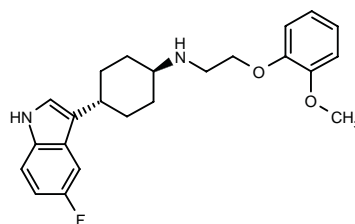
281697

trans-N-[4-(5-Fluoro-1H-indol-3-yl)cyclohexyl]-N-[2-(1H-indol-4-yloxy)ethyl]amine



C₂₄ H₂₆ F N₃ O; Mol wt: 391.4874

ACTION – Agent for the treatment of depression and anxiety that is reported to act concomitantly at 5-HT_{1A} autoreceptors and the 5-HT transporter (K_i = 1.08 and 2.50 nM, respectively). Another compound from this series of *N*-aryloxyethylamine derivatives is:



281698: C₂₃ H₂₇ F N₂ O₂

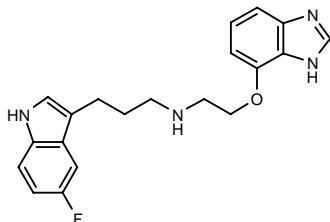
SOURCE – American Home Products.

REFERENCES

- Mewshaw, R.E. et al. (American Home Products Corp.) *N-Aryloxyethylamine derivs. for the treatment of depression*. WO 9951576.

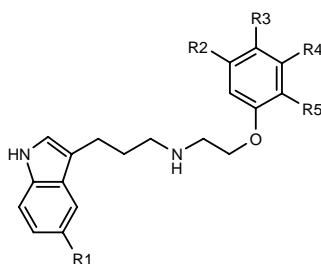
281785

N-[2-(1*H*-Benzimidazol-7-yloxy)ethyl]-*N*-[3-(5-fluoro-1*H*-indol-3-yl)propyl]amine



C₂₀H₂₁F N₄O; Mol wt: 352.4109

ACTION – Antidepressant that is reported to act concomitantly at 5-HT_{1A} autoreceptors and the 5-HT transporter (K_i = 0.69 and 0.39 nM, respectively). Other specifically claimed compounds from this series of *N*-aryloxyethyl-indolyl-alkylamines include the following:



Compound	R1	R2	R3	R4,R5	Formula
281786	H	H	H	-N=CHNH-	C ₂₀ H ₂₂ N ₄ O
281787	H	H	H	-NHCONH-	C ₂₀ H ₂₂ N ₄ O ₂
281788	H	H	H	-NHCSNH-	C ₂₀ H ₂₂ N ₄ OS
281789	F	Cl	H	-NHCH=N-	C ₂₀ H ₂₀ ClFN ₄ O
281790	H	H	F	-NHCONH-	C ₂₀ H ₂₁ FN ₄ O ₂

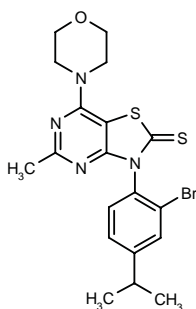
SOURCE – American Home Products.

REFERENCES

1. Mewshaw, R.E. and Nelson, J.A. (American Home Products Corp.) *N*-Aryloxyethyl-indolyl-alkylamines for the treatment of depression. WO 9951591.

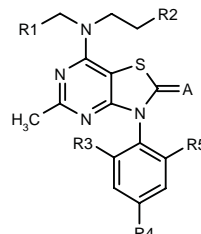
281845

3-(2-Bromo-4-isopropylphenyl)-5-methyl-7-(4-morpholin-yl)thiazolo[4,5-*d*]pyrimidine-2(3*H*)-thione



C₁₉H₂₁Br N₄O S₂; Mol wt: 465.4379

ACTION – Corticotropin-releasing factor (CRF) antagonist expected to have potential in the treatment of imbalances associated with abnormal levels of CRF in patients with depression, affective disorders and/or anxiety, among other conditions. Other specifically claimed thiazolo-[4,5-*d*]pyrimidines and pyridines include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
281846	Me	Et	Br	i-Pr	H	S	C ₂₁ H ₂₇ BrN ₄ S ₂
281847	Me	H	Me	Me	Me	S	C ₁₉ H ₂₄ N ₄ S ₂
281848	cyclopropyl	Me	Me	Me	Me	S	C ₂₂ H ₂₈ N ₄ S ₂
281849	Me	H	Me	Me	Me	O	C ₁₉ H ₂₄ N ₄ OS
281850	CH ₂ OMe	OMe	Me	Me	Me	O	C ₂₁ H ₂₈ N ₄ O ₃ S

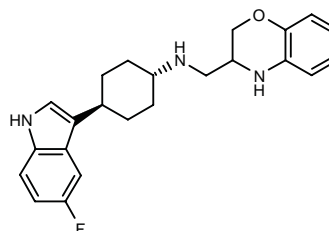
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Beck, J.P. (DuPont Pharmaceuticals Co.) Thiazolo[4,5-*d*]pyrimidines and pyridines as corticotropin releasing factor (CRF) antagonists. WO 9951608.

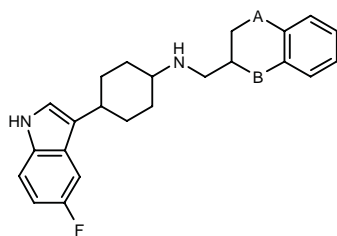
281924

trans-*N*-(3,4-Dihydro-2*H*-1,4-benzoxazin-3-ylmethyl)-*N*-[4-(5-fluoro-1*H*-indol-3-yl)cyclohexyl]amine



C₂₃H₂₆F N₃O; Mol wt: 379.4764

ACTION – Agent for the treatment of depression and anxiety that acts concomitantly at the 5-HT transporter (K_i = 10 nM against [³H]-paroxetine binding in rat frontal cortical membranes) and the 5-HT_{1A} autoreceptor (20% inhibition of [³H]-8-OH-DPAT binding to cloned human 5-HT_{1A} receptors expressed in CHO cells at 1 μM). Other specifically claimed compounds from this series of indol-3-yl-cyclohexyl amine derivatives include the following:



Compound	A	B	Isomer	Formula
281925	NH	O	cis	C ₂₃ H ₂₆ FN ₃ O
281926	NH	O	trans	C ₂₃ H ₂₆ FN ₃ O
281927	O	NH	cis	C ₂₃ H ₂₆ FN ₃ O

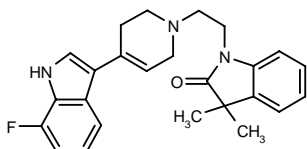
SOURCE – American Home Products.

REFERENCES

1. Mewshaw, R.E. and Zhou, P. (American Home Products Corp.) *Indol-3-yl-cyclohexyl amine derivs. for the treatment of depression (5-HT₁ receptor antagonist)*. WO 9951592.

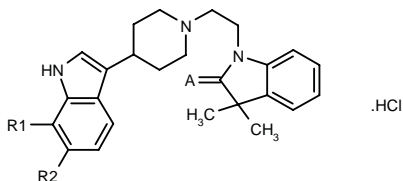
283162

1-[2-[4-(7-Fluoro-1*H*-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-3,3-dimethyl-2,3-dihydro-1*H*-indol-2-one

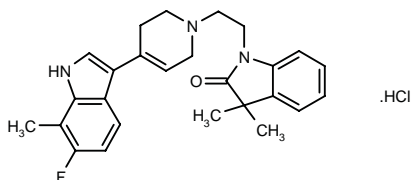


C₂₅ H₂₆ F N₃ O; Mol wt: 403.4984

ACTION – Serotonergic modulator that binds to 5-HT_{2A} receptors and inhibits 5-HT reuptake. The activity of the compound at the 5-HT_{2A} receptor was demonstrated by its ability to displace [³H]-ketanserin binding and its activity as a 5-HT reuptake inhibitor by its ability to displace [³H]-paroxetine binding at the reuptake site. Potentially useful in the treatment of depression, obesity, bulimia, alcoholism, pain, hypertension, memory loss, sexual dysfunction, anxiety, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, smoking cessation, drug addiction, emesis, Alzheimer's disease and sleep disorders. Other representative compounds from this series of indole derivatives are:



Compound	R1	R2	A	Formula
283164	F	H	O	C ₂₅ H ₂₆ FN ₃ O.HCl
283165	H	F	S	C ₂₅ H ₂₆ FN ₃ S.HCl



283163: C₂₆ H₂₈ F N₃ O . HCl

SOURCE – Lilly.

REFERENCES

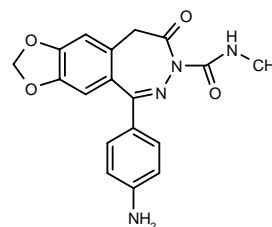
1. Fairhurst, J. et al. (Eli Lilly and Company, Ltd.) *Indole derivs. as 5-HT_{2A} ligands and as serotonin reuptake inhibitors*. EP 963983, WO 9958525.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

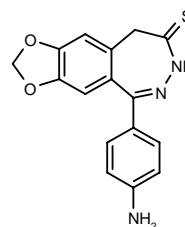
281752

5-(4-Aminophenyl)-*N*-methyl-8-oxo-8,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*][2,3]benzodiazepine-7-carboxamide



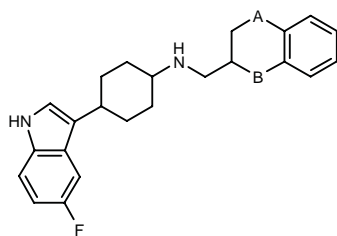
C₁₈ H₁₆ N₄ O₄; Mol wt: 352.3484

ACTION – Anticonvulsant proven active against seizures induced by both maximal electroshock and pentylene-tetrazol (ED₅₀ = 18.6 and 16.3 mg/kg i.p., respectively), as well as audiogenic seizures in mice (ED₅₀ = 12.4 and 8.7 mg/kg i.p. for the clonic and tonic phase, respectively). The anticonvulsant effect appeared to be mediated by an AMPA/kainate receptor-antagonist effect, as indicated by its ability to inhibit seizures induced by AMPA (ED₅₀ = 18.6 and 10.3 mg/kg i.p. for the clonic and tonic phase, respectively) or kainate (ED₅₀ = 8.61 mg/kg i.p.); its protective effect against audiogenic seizures was reversed by pretreatment with aniracetam. Anticonvulsant activity was observed at doses that did not cause sedation or ataxia, as demonstrated in the rotarod test in mice. Binding experiments carried out in rat brain synaptic membranes demonstrated that compound does not interfere with 5-HT₁, 5-HT₂, dopamine, norepinephrine and NMDA receptors, the glycine site on the NMDA receptor and metabotropic glutamate receptors. Another compound from this series of 2,3-benzodiazepine derivatives is:



281753: C₁₆ H₁₃ N₃ O₂ S

SOURCES – Università degli Studi di Catanzaro, Catanzaro (IT); Università degli Studi di Messina, Messina (IT); Università degli Studi di Milano, Milano (IT); Università degli Studi di Modena, Modena (IT).



Compound	A	B	Isomer	Formula
281925	NH	O	cis	C ₂₃ H ₂₆ FN ₃ O
281926	NH	O	trans	C ₂₃ H ₂₆ FN ₃ O
281927	O	NH	cis	C ₂₃ H ₂₆ FN ₃ O

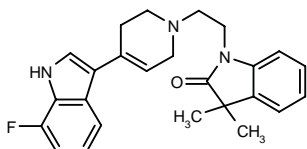
SOURCE – American Home Products.

REFERENCES

1. Mewshaw, R.E. and Zhou, P. (American Home Products Corp.) *Indol-3-yl-cyclohexyl amine derivs. for the treatment of depression (5-HT₁ receptor antagonist)*. WO 9951592.

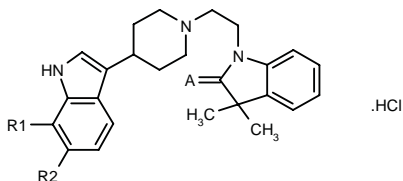
283162

1-[2-[4-(7-Fluoro-1*H*-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-3,3-dimethyl-2,3-dihydro-1*H*-indol-2-one

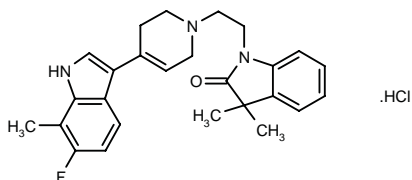


C₂₅ H₂₆ F N₃ O; Mol wt: 403.4984

ACTION – Serotonergic modulator that binds to 5-HT_{2A} receptors and inhibits 5-HT reuptake. The activity of the compound at the 5-HT_{2A} receptor was demonstrated by its ability to displace [³H]-ketanserin binding and its activity as a 5-HT reuptake inhibitor by its ability to displace [³H]-paroxetine binding at the reuptake site. Potentially useful in the treatment of depression, obesity, bulimia, alcoholism, pain, hypertension, memory loss, sexual dysfunction, anxiety, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, smoking cessation, drug addiction, emesis, Alzheimer's disease and sleep disorders. Other representative compounds from this series of indole derivatives are:



Compound	R1	R2	A	Formula
283164	F	H	O	C ₂₅ H ₂₆ FN ₃ O.HCl
283165	H	F	S	C ₂₅ H ₂₆ FN ₃ S.HCl



283163: C₂₆ H₂₈ F N₃ O . HCl

SOURCE – Lilly.

REFERENCES

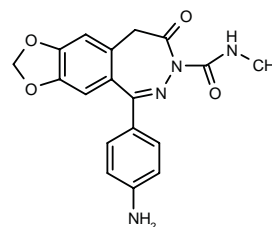
1. Fairhurst, J. et al. (Eli Lilly and Company, Ltd.) *Indole derivs. as 5-HT_{2A} ligands and as serotonin reuptake inhibitors*. EP 963983, WO 9958525.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

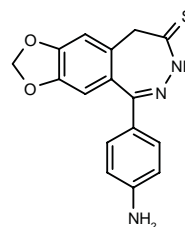
281752

5-(4-Aminophenyl)-*N*-methyl-8-oxo-8,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*][2,3]benzodiazepine-7-carboxamide



C₁₈ H₁₆ N₄ O₄; Mol wt: 352.3484

ACTION – Anticonvulsant proven active against seizures induced by both maximal electroshock and pentylenetetrazol (ED₅₀ = 18.6 and 16.3 mg/kg i.p., respectively), as well as audiogenic seizures in mice (ED₅₀ = 12.4 and 8.7 mg/kg i.p. for the clonic and tonic phase, respectively). The anticonvulsant effect appeared to be mediated by an AMPA/kainate receptor-antagonist effect, as indicated by its ability to inhibit seizures induced by AMPA (ED₅₀ = 18.6 and 10.3 mg/kg i.p. for the clonic and tonic phase, respectively) or kainate (ED₅₀ = 8.61 mg/kg i.p.); its protective effect against audiogenic seizures was reversed by pretreatment with aniracetam. Anticonvulsant activity was observed at doses that did not cause sedation or ataxia, as demonstrated in the rotarod test in mice. Binding experiments carried out in rat brain synaptic membranes demonstrated that compound does not interfere with 5-HT₁, 5-HT₂, dopamine, norepinephrine and NMDA receptors, the glycine site on the NMDA receptor and metabotropic glutamate receptors. Another compound from this series of 2,3-benzodiazepine derivatives is:



281753: C₁₆ H₁₃ N₃ O₂ S

SOURCES – Università degli Studi di Catanzaro, Catanzaro (IT); Università degli Studi di Messina, Messina (IT); Università degli Studi di Milano, Milano (IT); Università degli Studi di Modena, Modena (IT).

REFERENCES

1. Grasso, S. et al. *Synthesis and anticonvulsant activity of novel and potent 2,3-benzodiazepine AMPA/kainate receptor antagonists*. J Med Chem 1999, 42(21): 4414.

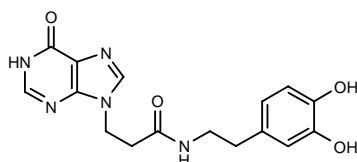
TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

AIT-203

282835

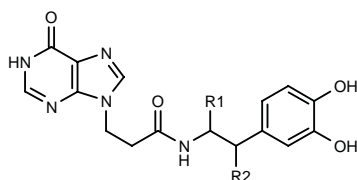
N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-(6-oxo-6,9-dihydro-1*H*-purin-9-yl)propionamide

N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-(hypoxanthin-9-yl)propionamide



C₁₆ H₁₇ N₅ O₄; Mol wt: 343.3413

ACTION – Small-molecule compound that efficiently crosses the blood–brain barrier, shown to inhibit MAO-A and -B with an IC₅₀ value of 6.0 μM, while exhibiting neither dopamine-agonist nor dopamine-antagonist effects. Potentially useful in the treatment of Parkinson's disease, depression, panic disorder, obsessive–compulsive disorder, chronic pain, peptic ulcer, irritable bowel syndrome, chronic fatigue, cataplexy, sleep apnea and migraine. Other specifically claimed 9-substituted hypoxanthines are:



Compound	R1	R2	Formula
AIT-297 [282836]	H	OH	C ₁₆ H ₁₇ N ₅ O ₅
AIT-201 [282837]	CO ₂ H	H	C ₁₇ H ₁₇ N ₅ O ₆

AIT-297 was also shown to be able to regulate calcium channel function.

SOURCE – NeoTherapeutics.

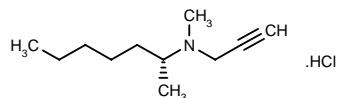
REFERENCES

1. Glasky, A.J. (NeoTherapeutics, Inc.) *Novel dopamine-like 9-substd. hypoxanthine and methods of use*. WO 9957119.

R-2HMP

281830

N-Methyl-*N*-[1(*R*)-methylhexyl]-*N*-(2-propynyl)amine hydrochloride



C₁₁ H₂₁ N . HCl; Mol wt: 203.7548

M.p. 130 °C.

ACTION – Orally active antiapoptotic agent with potent MAO-B-inhibitory activity both *in vitro* (IC₅₀ = 30 nM) and *in vivo* (ED₅₀ = 0.2 mg/kg i.p. for brain MAO-B inhibition in mice). Compound showed antiapoptotic activity in several *in vitro* models including ara-C-induced apoptosis in cerebellar granule cells (IC₅₀ = 1-10 nM), trophic factor withdrawal-induced apoptosis in PC12 cells, DSP-4-induced apoptosis in dopaminergic neuroblastoma SH-SY5Y cells (maximal rescue at 1 μM), and in hippocampal slices incubated under hypoxic/hypoglycemic conditions. *In vivo*, compound exhibited dose-related protection from hippocampal CA1 lesions induced by transient cerebral ischemia in rats both after s.c. (ED₅₀ = 20-200 μg/kg) and oral dosing (doubling of neuronal survival at 1 mg/kg). Moreover, compound was able to increase neuronal survival in the kainic acid-induced seizure model in rats (0.02 mg/kg s.c.), in the mouse MPTP model of Parkinson's disease (significant increase at 0.2 mg/kg b.i.d. for 18 days) and against MK-801-induced neuronal death in the retrosplinal cortex of adult rats (significant protection at 0.25 mg/kg i.p.). Compound was also able to protect normal R2 rat fibroblasts from cisplatin toxicity, to increase the sensitivity of tumorigenic NW16 cells to cisplatin, as well as to protect *in vivo* bone marrow cells from cisplatin (at 0.38 μg/kg i.p.). It showed a favorable pharmacokinetic profile after both s.c. and oral administration in rats and was well tolerated after several months of chronic administration to mice, rats and dogs. Promising agent for the treatment of neurodegenerative disorders including Parkinson's disease and stroke.

SOURCE – University of Saskatchewan, Saskatoon, SK (CA).

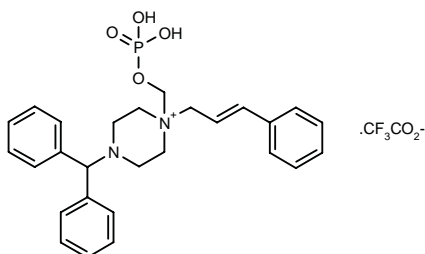
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TREATMENT OF NAUSEA AND VOMITING

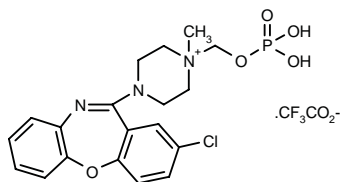
279501

4-(Diphenylmethyl)-1-[3-phenylprop-2(*E*)-enyl]-1-(phosphonooxymethyl)piperazin-1-ium trifluoroacetate



C27 H32 N2 O4 P . C2 F3 O2; Mol wt: 592.5478

ACTION – *N*-Phosphonooxymethyl cinnarizine prodrug that is rapidly and completely converted to parent drug in rats and dogs after i.v. administration. In comparison to parent drug, the prodrug showed markedly improved water solubility and very good chemical stability at physiological pH. Among others, the ***N*-phosphonooxymethyl prodrug of loxapine** showed similar properties.



279503: C19 H22 Cl N3 O5 P . C2 F3 O2

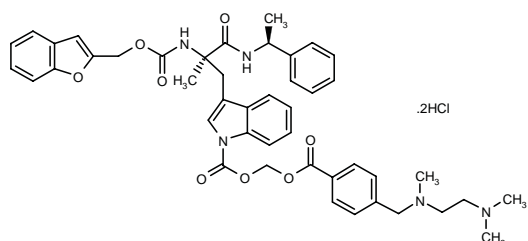
SOURCE – University of Kansas, Lawrence, KS (US).

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2. Krise, J.P. et al. A novel prodrug approach for tertiary amines. 3. In vivo evaluation of two *N*-phosphonooxymethyl prodrugs in rats and dogs. *J Pharm Sci* 1999, 88(9): 928.
3. Krise, J.P. et al. Novel prodrug approach for tertiary amines: Synthesis and preliminary evaluation of *N*-phosphonooxymethyl prodrugs. *J Med Chem* 1999, 42(16): 3094.

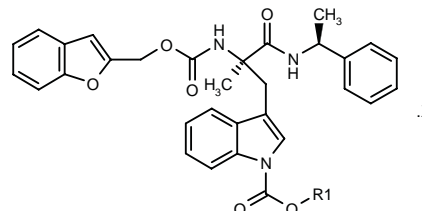
281975

3-[2(*R*)-(1-Benzofuran-2-ylmethoxycarboxamido)-2-[*N*-[1(*S*)-phenylethyl]carbamoyl]propyl]-1 *H*-indole-1-carboxylic acid [4-[*N*-[2-(dimethylamino)ethyl]-*N*-methylaminomethyl]benzoyloxy]methyl ester dihydrochloride



C45 H49 N5 O8 . 2HCl; Mol wt: 860.8309

ACTION – Water-soluble prodrug of the tachykinin NK₁ receptor antagonist PD-154075⁺, with potential in the treatment of emesis, respiratory disorders, inflammation, gastrointestinal disorders, ophthalmic conditions, allergies, migraine, inflammatory or neurogenic pain and atherosclerosis. In addition to increased water solubility and good stability in solution, compound exhibited a conversion rate to the parent compound of 104.0 ± 38.2% after i.v. administration and a bioavailability of the parent compound of 46.4 ± 4.2% after p.o. administration in rats. Other exemplified prodrugs include the following:



Compound	R1	X	Formula
281978	4-(4-Me-1-Piz-CH2)-PhCOOCH2	2HCl	C ₄₅ H ₄₇ N ₅ O ₈ ·2HCl
281979	4-[4-(HOCH2CH2)-1-Piz-CH2]-PhCOOCH2	2HCl	C ₄₆ H ₄₉ N ₅ O ₉ ·2HCl
281980	4-(1-Piz-CH2)-PhCOOCH2	2HCl	C ₄₄ H ₄₅ N ₅ O ₈ ·2HCl
281981	2-[N(Me)2CH2COOCH2]-Ph	HCl	C ₄₂ H ₄₂ N ₄ O ₈ ·HCl

SOURCE – Warner-Lambert.

REFERENCES

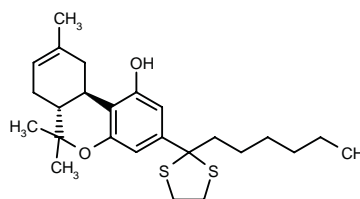
1. Chan, O.H. et al. (Warner-Lambert Co.) *Prodrugs of benzofuranylmethyl carbamate NK1 antagonists*. WO 9952903.

*Drug Data Rep 1997, 019(03): 0214.

AMG-3

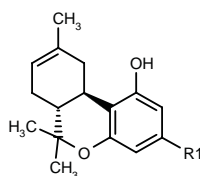
283138

3-(2-Hexyl-1,3-dithiolan-2-yl)-6,6,9-trimethyl-6a(*R*),7,10,10a(*R*)-tetrahydro-6*H*-dibenzo[*b,d*]pyran-1-ol



C25 H36 O2 S2; Mol wt: 432.6894

ACTION – Cannabinoid receptor agonist with improved binding affinity for the CB₁ and CB₂ receptors compared with known cannabinoids (K_i values of 0.32 nM for the CB₁ receptor and 1.7 nM for the CB₂ receptor, compared to respective values of 45 and 14 nM for Δ⁸-tetrahydrocannabinol). It is expected to produce fewer side effects than known agonists due to its greater potency and higher selectivity. Potentially useful for the prevention of tissue rejection in organ transplant recipients, in the treatment of glaucoma, autoimmune diseases (e.g., lupus erythematosus, rheumatoid arthritis, psoriasis, multiple sclerosis and inflammatory bowel disease), for controlling nausea in patients undergoing chemotherapy and for enhancing appetite and controlling pain in individuals with AIDS wasting syndrome. Other exemplified cannabinoids include the following:



Compound	R1	Formula
AM-407 [283139]	1-Me-4-Pr-cyclohexyl	C ₂₆ H ₃₈ O ₂
AMG-9 [283140]	2-(C6H13)-1,3-dithian-2-yl	C ₂₆ H ₃₈ O ₂ S ₂
AMG-14 [283141]	2-(C6H13)-1,3-dioxolan-2-yl	C ₂₅ H ₃₆ O ₄
AM-411 [283142]	1-adamantyl	C ₂₆ H ₃₄ O ₂
AM-732 [283143]	1,7,7-(Me)3-bicyclo[2.2.1]hept-2-yl	C ₂₆ H ₃₆ O ₂

SOURCE – University of Connecticut, Storrs, CT (US).

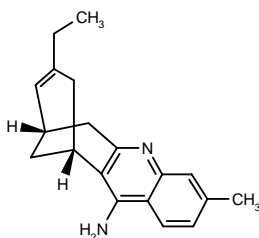
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COGNITION-ENHANCING DRUGS

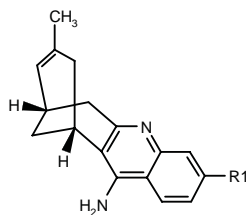
280026

12-Amino-9-ethyl-3-methyl-6,7,10,11-tetrahydro-7(S),11(S)-methanocycloocta[b]quinoline



C₁₉ H₂₂ N₂; Mol wt: 278.3968

ACTION – Acetylcholinesterase inhibitor, a tacrine–huperzine A hybrid molecule with improved activity versus the parent compounds (IC₅₀ = 4.5, 74 and 130 nM for compound, huperzine A and tacrine, respectively) and selectivity over butyrylcholinesterase (IC₅₀ = 347 nM). Compound reversed neuromuscular blockade induced by *d*-tubocurarine in peripheral cholinergic synapses with an AI₅₀ (drug concentration that reaches 50% of antagonism index) of 213 nM. Potentially useful for the treatment of cholinergic deficits in Alzheimer's disease. Other tacrine–huperzine A hybrids include the following:



Compound	R1	Formula
280027	F	C ₁₇ H ₁₇ FN ₂
280028	H	C ₁₇ H ₁₈ N ₂

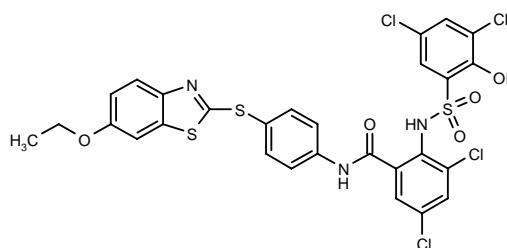
SOURCE – Medichem.

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2. Camps, P. et al. *Synthesis, in vitro pharmacology, and molecular modeling of very potent tacrine - huperzine A hybrids as acetylcholinesterase inhibitors of potential interest for the treatment of Alzheimer's disease*. J Med Chem 1999, 42(17): 3227.

280656

3,5-Dichloro-2-(3,5-dichloro-2-hydroxyphenylsulfonamido)-N-[4-(6-ethoxybenzothiazol-2-ylsulfanyl)phenyl]-benzamide



C₂₈ H₁₉ Cl₄ N₃ O₅ S₃; Mol wt: 715.4841

M.p. 164 °C.

ACTION – Small-molecule cathepsin D inhibitor (IC₅₀ = 250 nM) potentially useful for the treatment of Alzheimer's disease and breast and ovarian cancer.

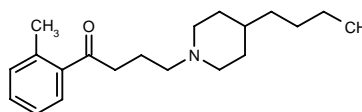
SOURCE – Bayer.

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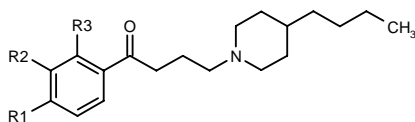
281591

4-(4-Butylpiperidin-1-yl)-1-(2-methylphenyl)butan-1-one



C₂₀ H₃₁ N O; Mol wt: 301.4709

ACTION – Agent for the treatment of conditions associated with reduced levels of acetylcholine such as neurodegenerative diseases and cognitive impairment, as well as for the treatment of glaucoma, a selective muscarinic M₁ receptor agonist with no significant affinity for M₂, M₃, M₄ and M₅ muscarinic receptors, α -adrenoceptor subtypes α_{1D} , α_{1B} , α_{1A} , α_{2A} , α_{2B} and α_{2C} , histamine H₁ or 5-HT_{1A} and 5-HT_{2A} receptor subtypes. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
281592	H	H	OEt	C ₂₁ H ₃₃ NO ₂
281593	H	H	OH	C ₁₉ H ₂₉ NO ₂
281594	H	Me	Me	C ₂₁ H ₃₃ NO
281595	Me	H	Me	C ₂₁ H ₃₃ NO
281596	H	H	OMe	C ₂₀ H ₃₁ NO ₂
281597	H	H	H	C ₁₉ H ₂₉ NO

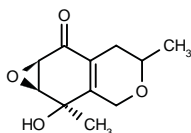
SOURCE – Acadia.

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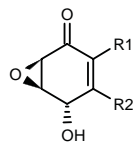
281634

2,5-Dimethyl-2(*R*)-hydroxy-1a(*S*),2,3,5,6,7a(*R*)-hexahydrooxireno[*g*][2]benzopyran-7-one

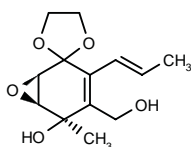


C₁₁ H₁₄ O₄; Mol wt: 210.2276

ACTION – An inhibitor of Fas-induced apoptosis produced by *Paecilomyces musicola* Matsushima 1975 RF-13867 (P-16450), potentially useful in the treatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, amyotrophic lateral sclerosis, cerebral ischemia, AIDS, dilated cardiomyopathy, myocardial infarction, etc. Other compounds obtained from the same source are:



Compound	R1	R2	Formula
281636	vinyl	CH ₂ OH	C ₉ H ₁₀ O ₄
281639	-CH ₂ CH(Me)OCH ₂ -		C ₁₀ H ₁₂ O ₄
281640	Pr	Me	C ₁₀ H ₁₄ O ₃
281641	(<i>Z</i>)-CH=CH ₂	CH ₂ OH	C ₁₁ H ₁₄ O ₄
281642	-CH[CH(OH)Me]OCH ₂ -		C ₁₀ H ₁₂ O ₅



281638: C₁₃ H₁₈ O₅

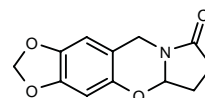
SOURCE – Shionogi.

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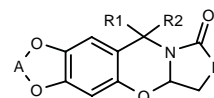
281746

5a,6,7,8-Tetrahydro-10*H*-1,3-dioxolo[4,5-*g*]pyrrolo[2,1-*b*]-[1,3]benzoxazin-8-one



C₁₂ H₁₁ N O₄; Mol wt: 233.2219

ACTION – Agent that enhances synaptic responses mediated by AMPA receptors with enhanced bioavailability and increased metabolic stability compared to related ampakines. *In vitro* activity was demonstrated by a 25% increase in the amplitude of excitatory postsynaptic potentials (EPSPs) in rat hippocampus slices at 300 μM. Compound exhibited an oral bioavailability of 100% and a half-life of 58 min following i.v. administration in rats. Potentially useful for the treatment of memory impairment, as well as for facilitating learning and enhancing memory in nonimpaired subjects. Other compounds within this series of acylbenzoxazines include the following:



Compound	R1	R2	A	B	Formula
281747	H	H	-(CH ₂) ₂ -	-CH ₂ -	C ₁₃ H ₁₃ NO ₄
281748	H	H	-(CH ₂) ₂ -	-(CH ₂) ₂ -	C ₁₄ H ₁₅ NO ₄
281749	-O-		-CH ₂ -	-CH ₂ -	C ₁₂ H ₉ NO ₅

SOURCE – University of California, Oakland, Oakland, CA (US).

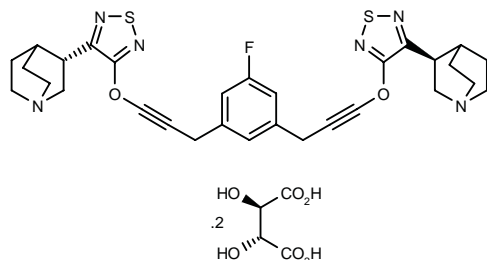
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283586

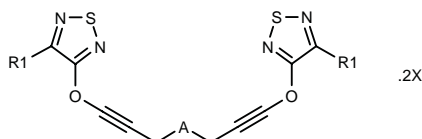
1,3-Bis[3-[4-[quinuclidin-3(S)-yl]-1,2,5-thiadiazol-3-yloxy]-2-propynyl]-5-fluorobenzene bis(L-tartrate)

3(S),3'(S)-(5-Fluoro-1,3-phenylene)bis(1-propyne-3,1-diyl)bis(oxy)bis(1,2,5-thiadiazol-4,3-diyl)bis(quinuclidine) bis(L-tartrate)



C30 H31 F N6 O2 S2 . 2 C4 H6 O6; Mol wt: 890.9157

ACTION – Muscarinic acetylcholine receptor agonist with an IC_{50} value of 0.70 nM for inhibition of [3H]-oxotremorine-M binding in rat cortical homogenates. Potentially useful in the treatment of Alzheimer's disease, cognitive dysfunction, severe painful conditions, glaucoma, psychosis, schizophrenia, bladder dysfunction, anxiety, sleep disorders and other conditions associated with cholinergic system malfunction. Other specifically claimed heterocyclic compounds are:



Compound	R1	A	X	Formula
283589	(5R,6R)-1-aza-bicyclo[3.2.1]oct-6-yl	-1,3-Ph-	L-tartrate	C ₃₀ H ₃₂ N ₆ O ₂ S ₂ .2C ₄ H ₆ O ₆
283592	3(S)-quinuclidinyl	-1,3-Ph-	L-tartrate	C ₃₀ H ₃₂ N ₆ O ₂ S ₂ .2C ₄ H ₆ O ₆
283593	(5R,6R)-1-aza-bicyclo[3.2.1]oct-6-yl	-1,4-Ph-	HCl	C ₃₀ H ₃₂ N ₆ O ₂ S ₂ .2HCl
283596	3(S)-quinuclidinyl	-1,4-Ph-	L-tartrate	C ₃₀ H ₃₂ N ₆ O ₂ S ₂ .2C ₄ H ₆ O ₆
283597	(5R,6R)-1-aza-bicyclo[3.2.1]oct-6-yl	-5-F-1,3-Ph-	L-tartrate	C ₃₀ H ₃₁ FN ₆ O ₂ S ₂ .2C ₄ H ₆ O ₆

SOURCE – Novo Nordisk.

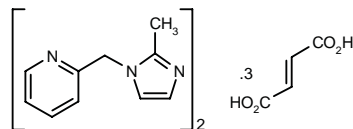
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NDD-094**275326**

Bis[2-(2-methylimidazol-1-ylmethyl)pyridine] trifumarate

SDZ-NDD-094



2 C10 H11 N3 . 3 C4 H4 O4; Mol wt: 694.6506

ACTION – Putative neurotrophic enhancer shown to significantly ameliorate the sensorimotor deficit on the side ipsilateral to the lesion following transient middle cerebral artery occlusion in rats at a dose of 10 mg/kg i.p. for 6 days, whereas it had no effect on the contralateral side or on infarct volume. Currently undergoing phase II clinical trials as a potential treatment for Alzheimer's disease.

SOURCE – Novartis.

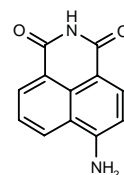
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TREATMENT OF CEREBROVASCULAR DISEASES

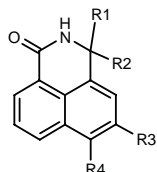
264954

6-Amino-2,3-dihydro-1H-benzo[de]isoquinoline-1,3-dione



C12 H8 N2 O2; Mol wt: 212.2072

ACTION – PARP (poly[ADP-ribose] polymerase or NAD⁺ ADP-ribosyltransferase) inhibitor (IC_{50} = 0.09 μ M against recombinant human enzyme) demonstrating neuroprotective effects in a rat model of focal cerebral ischemia. Potentially useful for the treatment of neurological and neurodegenerative disorders including cerebral ischemia, reperfusion injury, traumatic brain injury, Alzheimer's disease and Parkinson's disease, as well as for arthritis, diabetes, inflammatory bowel diseases, cardiovascular disorders, septic shock and cancer. Other exemplified fused tricyclic compounds are:



Compound	R1	R2	R3	R4	Formula
283709		-O-	H	H	C ₁₂ H ₇ NO ₂
283710	H	H	H	H	C ₁₂ H ₉ NO
283711		-O-	H	SO ₃ K	C ₁₂ H ₆ KNO ₅ S
283712		-O-	H	Cl	C ₁₂ H ₆ ClNO ₂
283713		-O-	H	SCH ₂ CH ₂ OH	C ₁₄ H ₁₁ NO ₃ S
283714		-O-	OH	H	C ₁₂ H ₇ NO ₃

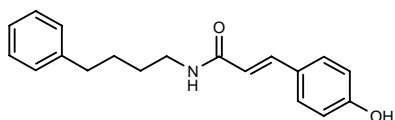
SOURCE – Guilford.

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280001

3-(4-Hydroxyphenyl)-N-(4-phenylbutyl)-2(E)-propenamide



C₁₉ H₂₁ N O₂; Mol wt: 295.3799

M.p. 140-1 °C.

ACTION – Potent NR1A/2B subtype-selective NMDA receptor antagonist (IC_{50} = 77 nM) with more than 1000-fold selectivity over NR1A/2A and NR1A/2C subtypes, as demonstrated by electrical recordings in *Xenopus oocytes* expressing cloned NMDA receptor subunits. Compound did not show affinity for α_1 -adrenoceptors (IC_{50} > 100 μ M) and its inhibitory activity against NR1A/2B receptors did not correlate with inhibition of epidermal growth factor (EGF) receptor and ErbB2/neu tyrosine kinase activity. Potentially useful for the treatment of neurological disorders including cerebral ischemia and Parkinson's disease.

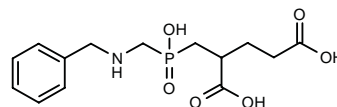
SOURCES – CoCensys; University of Oregon, Eugene, OR (US); Parke-Davis (Warner-Lambert).

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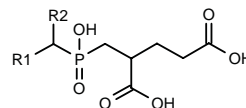
281685

2-[(Benzylaminomethyl)(hydroxy)phosphorylmethyl]-glutaric acid



C₁₄ H₂₀ N O₆ P; Mol wt: 329.2870

ACTION – An inhibitor of *N*-acetylated α -linked acidic dipeptidase (NAALADase; K_i = 51.8 nM) found to protect against ischemic insult in cortical cell cultures with an EC_{50} of 0.9 nM. Potentially useful in the treatment of stroke, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, alcoholism and nicotine dependence, as well as prostate disorders, particularly prostate cancer. Other exemplified phosphinic acid derivatives include the following:



Compound	R1	R2	Formula
281686	Ph	NHCH ₂ Ph	C ₂₀ H ₂₄ NO ₆ P
281687	H	1,3-dioxo-2-isindolyl	C ₁₅ H ₁₆ NO ₆ P
281688	H	NHPh	C ₁₃ H ₁₈ NO ₆ P
281689	H	NHSO ₂ Ph	C ₁₃ H ₁₈ NO ₆ PS
281690	H	4-F-PhNH	C ₁₃ H ₁₇ FNO ₆ P
281691	H	4-MeO-PhNH	C ₁₄ H ₂₀ NO ₇ P
281692	H	4-Me-PhNH	C ₁₄ H ₂₀ NO ₆ P
281693	H	4-t-Bu-PhNH	C ₁₇ H ₂₆ NO ₆ P

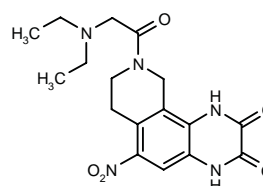
SOURCE – Guilford.

REFERENCES

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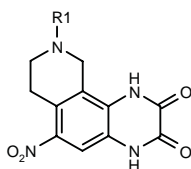
282248

9-[2-(Diethylamino)acetyl]-6-nitro-1,2,3,4,7,8,9,10-octahydropyrido[3,4-f]quinoxaline-2,3-dione



C₁₇ H₂₁ N₅ O₅; Mol wt: 375.3829

ACTION – Excitatory amino acid antagonist with potential in the treatment of disorders responsive to the blockade of aspartate, glutamate or kainate receptors such as epilepsy, anxiety, schizophrenia, depression, neuropathic pain, neurodegenerative disorders, cerebral hypoxia/ischemia, or stress-related psychiatric disorders. Other specifically claimed compounds from this series of fused azacyclic quinoxalinediones include the following:



Compound	R1	Formula
282249	CO(CH ₂) ₃ N(Me) ₂	C ₁₇ H ₂₁ N ₅ O ₅
282250	COCH ₂ CH ₂ N(Et) ₂	C ₁₈ H ₂₃ N ₅ O ₅
282251	CSNHPh	C ₁₈ H ₁₅ N ₅ O ₄ S
282252	2-(2H-5-tetrazolyl)-PhCO	C ₁₉ H ₁₄ N ₈ O ₅
282253	2-thienyl-SO ₂	C ₁₅ H ₁₂ N ₄ O ₆ S ₂
282254	1-Me-4-imidazolyl-SO ₂	C ₁₅ H ₁₄ N ₆ O ₆ S
282255	CH ₂ CONH(CH ₂) ₃ CO ₂ Me	C ₁₈ H ₂₁ N ₅ O ₇
282256	CH ₂ CONHCH ₂ CH ₂ Ph	C ₂₁ H ₂₁ N ₅ O ₅
282257	(CH ₂) ₃ CN	C ₁₅ H ₁₅ N ₅ O ₄
282258	CH ₂ CONH(CH ₂) ₃ CO ₂ H	C ₁₇ H ₁₉ N ₅ O ₇

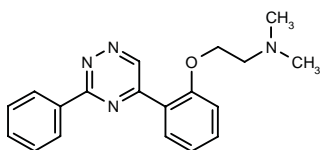
SOURCE – Warner-Lambert.

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1. Bigge, C.F. et al. (Warner-Lambert Co.) *Excitatory amino acid antagonists: Fused azacyclic quinoxalinediones and immunoassays thereof*. US 5968928.

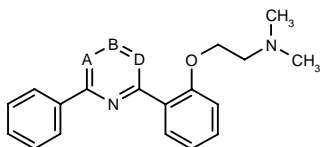
282317

N,N-Dimethyl-*N*-[2-[2-(3-phenyl-1,2,4-triazin-5-yl)phenoxy]ethyl]amine



C₁₉H₂₀N₄O; Mol wt: 320.3940

ACTION – AMPA receptor antagonist and high-affinity ligand for the Na⁺ channel site 2 (K_i = 2.4 μM), proven to inhibit kainate-induced currents in neuronal cells by 98% at 100 μM. Potentially useful in the treatment of neurodegenerative disorders, as well as the sequelae of cerebral ischemia. Other exemplified compounds include the following:



Compound	A	B	D	Formula
282318	N	CH	CH	C ₂₀ H ₂₁ N ₃ O
282319	N	CH	N	C ₁₉ H ₂₀ N ₄ O
282320	CH	N	N	C ₁₉ H ₂₀ N ₄ O

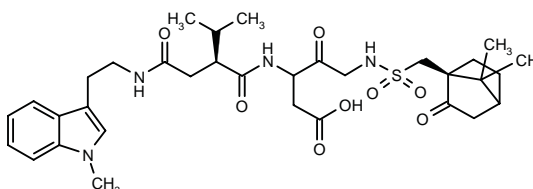
SOURCE – Boehringer Ingelheim.

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1. Brenner, M. et al. (Boehringer Ingelheim Pharma KG;Boehringer Ingelheim Italia SpA) *Novel diphenyl-substd. 6-ring-heterocycles, methods for producing them and their use as medicaments*. WO 9954311.

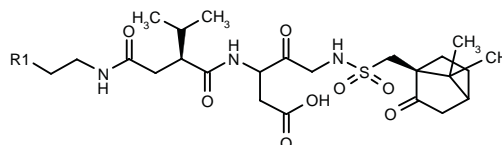
283153

5-[7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1(*S*)-ylmethylsulfonamido]-3-[3-methyl-2(*S*)-[*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]carbamoylmethyl]butyramido]-4-oxopentanoic acid



C₃₃H₄₆N₄O₈S; Mol wt: 658.8124

ACTION – IL-1β-converting enzyme (ICE, or caspase 1) inhibitor proven to inhibit the enzyme with K_i and IC₅₀ values of 0.0004 and 0.0059 μM, respectively, versus an IC₅₀ for Ich2 (caspase 4) of 1.24 μM; cellular activity was also demonstrated against ICE in human peripheral blood mononuclear cells (PMBCs; IC₅₀ = 0.24 μM). Compound is expected to be useful for the treatment of stroke, inflammatory disorders, septic shock, reperfusion injury, Alzheimer's disease, shigellosis and multiple sclerosis. Other exemplified succinamide derivatives include the following:



Compound	R1	Formula
283154	7-Me-3-indolyl	C ₃₃ H ₄₆ N ₄ O ₈ S
283155	1-benzimidazolyl	C ₃₁ H ₄₃ N ₅ O ₈ S

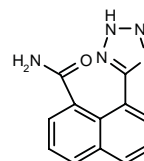
SOURCES – BASF; Warner-Lambert.

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1. Caprathe, B.W. et al. (Warner-Lambert Co.;BASF AG) *Succinamide inhibitors of interleukin-1β converting enzyme*. WO 9956765.

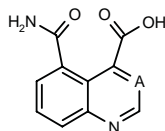
283364

8-(2*H*-Tetrazol-5-yl)naphthalene-1-carboxamide

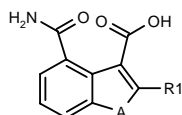


C₁₂H₉N₅O; Mol wt: 239.2371

ACTION – PARP (poly[ADP-ribose] polymerase, or NAD⁺ ADP-ribosyltransferase) inhibitor (IC₅₀ = 100 µM or less), potentially useful in the treatment of neurological disorders and neurodegenerative diseases, inflammatory bowel disease, cardiovascular disorders, septic shock, cancer, arthritis and diabetes. Other specifically claimed carboxamide compounds include the following:



Compound	A	Formula
283366	CH	C ₁₁ H ₈ N ₂ O ₃
283368	N	C ₁₀ H ₇ N ₃ O ₃



Compound	R1	A	Formula
283371	Me	N(Ac)	C ₁₃ H ₁₂ N ₂ O ₄
283372	H	O	C ₁₀ H ₇ NO ₄
283374	H	S	C ₁₀ H ₇ NO ₃ S
283375	Me	N(Me)	C ₁₂ H ₁₂ N ₂ O ₃

SOURCE – Guilford.

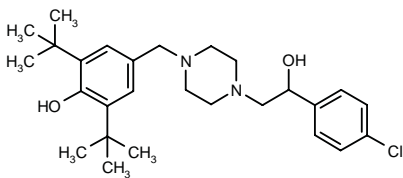
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- Li, J.-H. and Zhang, J. (Guilford Pharmaceuticals Inc.) *Carboxamide cpds., compsns., and methods for inhibiting PARP activity*. WO 9959973.

AM-36

241376

4-[4-[2-(4-Chlorophenyl)-2-hydroxyethyl]piperazin-1-ylmethyl]-2,6-bis(*tert*-butyl)phenol



C27 H39 Cl N2 O2; Mol wt: 459.0701

ACTION – Neuroprotective agent, a polyamine-site NMDA receptor antagonist with neuronal sodium and calcium channel-blocking and antioxidant activity. AM-36 exhibited neuroprotective activity both *in vitro* against neurotoxicity induced by NMDA or veratridine in neuronal cell cultures (IC₅₀ = 0.4 and 1.3 µM, respectively), and *in vivo* in two models of cerebral stroke; in a model of glutamate toxicity in mouse striatum, compound (60 mg/kg i.v.) completely prevented the loss of striatal tyrosine hydroxylase induced by subchronic administration of methamphetamine, and in the rat ET-1 middle cerebral artery model of ischemia, compound (1.8 mg/kg i.p. once daily for 2 days given within 30 min of the onset of stroke) produced a marked reduction in infarct area.

SOURCES – Amrad; Monash University, Clayton (AU).

REFERENCES

- Jarrott, B. et al. (Monash University) *Arylalkylpiperazine cpds. as antioxidants*. WO 9743259.
- Callaway, J.K. et al. *Delayed treatment with AM-36, a novel neuroprotective agent, reduces neuronal damage after endothelin-1-induced middle cerebral artery occlusion in conscious rats*. Stroke 1999, 30(12): 2704.
- Jarrott, B. et al. *Development of a novel arylalkylpiperazine compound (AM-36) as a hybrid neuroprotective drug*. Drug Dev Res 1999, 46(3-4): 261.
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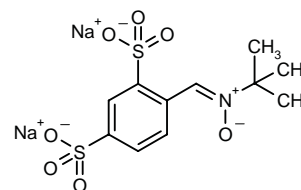
NXY-059

259634

4-(*tert*-Butyliminiomethyl)benzene-1,3-disulfonic acid *N*-oxide disodium salt

N-(*tert*-Butyl)-α-(2,4-disulfophenyl)nitron disodium salt

CPI-22



C11 H13 N Na2 O7 S2; Mol wt: 381.3357

ACTION – Neuroprotective agent, a nitron with free radical-trapping properties able to improve neurological deficits and reduce brain infarct volume in models of focal ischemia induced by both transient and permanent middle cerebral artery occlusion (MCAO) in rats. In transient MCAO, compound administered 1 h after reperfusion at doses of 0.3, 3 or 30 mg/kg by i.v. bolus followed by 0.3, 3 and 3 mg/kg/h i.v. for 24 h reduced infarct volume (50% at all doses) and neurological deficits at 24 and 48 h after recirculation; the parent compound PBN at a dose equimolar to 3 mg/kg failed to affect infarct volume. Compound was also effective after 7 days of recovery from transient MCAO and showed a therapeutic window of 3-6 h after starting reperfusion. In a permanent MCAO model, compound administered at a dose of 100 mg/kg i.p. at 30 min after MCAO, followed by i.v. infusion of 4.17 mg/kg/h for 23 h, decreased median infarct volume by 76%. NXY-059 does not easily pass through the blood-brain barrier and appears to act by attenuating radical oxygen species (ROS)-mediated reperfusion injury by interfering with the interaction between inflammatory cells and endothelium, or by direct effect on ROS produced by circulating inflammatory or endothelial cells. It is in phase II clinical trials for stroke.

SOURCES – AstraZeneca; Centaur; University of Kentucky, Lexington, KY (US); Oklahoma Medical Research Foundation, Oklahoma City, OK (US).

REFERENCES

- Carney, J.M. (Oklahoma Medical Research Foundation; University of Kentucky) *2,4-Disulfo phenyl butyl nitron, its salts and their use as pharmaceuticals*. US 5780510.

2. Carney, J.M. (Oklahoma Medical Research Foundation;University of Kentucky) *2,4-Disulfonyl phenyl butyl nitron, its salts, and their use as pharmaceuticals*. WO 9517876.

3. Green, A.R. and Ashwood, T. *Experimental and clinical experiences with clomethiazole, NXY-059 and AR-R15896*. Eur Neuropsychopharmacol 1999, 9(Suppl. 5): Abst S.23.05.

4. Kuroda, S. et al. *Neuroprotective effects of a novel nitron, NXY-059, after transient focal cerebral ischemia in the rat*. J Cereb Blood Flow Metab 1999, 19(7): 778.

5. Maples, K. et al. *NXY-059: Neuroprotective effects in rat focal stroke models*. Soc Neurosci Abst 1999, 25(Part 1): Abst 235.15.

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7. *AstraZeneca takes an ambitious approach to drug R&D*. DailyDrugNews.com (Daily Essentials) 1999, Dec 13.

8. *Centaur comments on NXY-059 development*. DailyDrugNews.com (Daily Essentials) 1999, Dec 16.

9. *Centaur conducts phase IIa trials on two product candidates in Q2 1999*. DailyDrugNews.com (Daily Essentials) 1999, Aug 17.

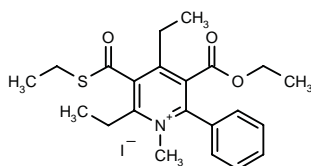
10. *Major innovations fuel R&D at Astra*. DailyDrugNews.com (Daily Essentials) 1998, Jan 28.

RESPIRATORY DRUGS

ASTHMA THERAPY

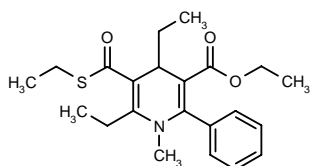
281391

3-(Ethoxycarbonyl)-5-(ethylsulfanylcarbonyl)-4,6-diethyl-1-methyl-2-phenylpyridinium iodide



C22 H28 I N O3 S; Mol wt: 513.4332

ACTION – Adenosine A_3 receptor antagonist with nanomolar affinity for the human A_3 receptor ($K_i = 219$ nM) and high selectivity over rat A_1 and A_{2A} receptors ($K_i = 31,900$ and $11,600$ nM, respectively), as well as over the human A_{2B} receptor ($K_i > 30$ μ M). In an *in vitro* functional test, compound showed pure antagonist activity against agonist (IB-MECA)-induced inhibition of adenylate cyclase in CHO cells ($K_B = 399$ nM). In the presence of rat brain homogenates, compound could be generated through oxidation of the precursor **281961** with similar adenosine A_3 receptor affinity ($K_i = 379$ nM) and selectivity ($K_i = 28.4$ μ M for rat A_1 receptors and > 100 μ M for rat A_2 receptors). Potentially useful as an antiinflammatory, antiasthmatic and antiischemic agent.



281961: C22 H29 N O3 S

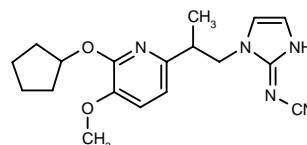
SOURCE – National Institutes of Health, Bethesda, MD (US).

REFERENCES

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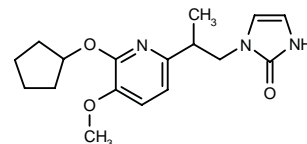
281584

1-[2-(6-Cyclopentyloxy-5-methoxypyridin-2-yl)propyl]-2,3-dihydro-1H-imidazol-2-ylidenecyanamide



C18 H23 N5 O2; Mol wt: 341.4127

ACTION – Agent for the treatment of allergic, atopic and inflammatory disorders with phosphodiesterase type 4 (PDE4; 25% of enzyme activity vs. control when tested against recombinant human mononuclear lymphocyte PDE4B at 0.1 μ M) and cytokine-inhibitory activity, and which is reported to be free of gastrointestinal side effects. Another specifically claimed compound from this series of pyridine derivatives is:



281585: C17 H23 N3 O3

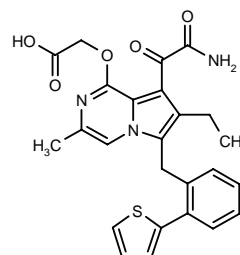
SOURCE – Janssen.

REFERENCES

1. Freyne, E.J.E. et al. (Janssen Pharmaceutica NV) *PDE IV inhibiting pyridine derivs*. WO 9950262.

281851

2-[8-(2-Amino-2-oxoacetyl)-7-ethyl-3-methyl-6-[2-(2-thienyl)benzyl]pyrrolo[1,2-a]pyrazin-1-yloxy]acetic acid



C25 H23 N3 O5 S; Mol wt: 477.5387

2. Carney, J.M. (Oklahoma Medical Research Foundation; University of Kentucky) *2,4-Disulfonyl phenyl butyl nitrone, its salts, and their use as pharmaceuticals*. WO 9517876.

3. Green, A.R. and Ashwood, T. *Experimental and clinical experiences with clomethiazole, NXY-059 and AR-R15896*. Eur Neuropsychopharmacol 1999, 9(Suppl. 5): Abst S.23.05.

4. Kuroda, S. et al. *Neuroprotective effects of a novel nitrone, NXY-059, after transient focal cerebral ischemia in the rat*. J Cereb Blood Flow Metab 1999, 19(7): 778.

5. Maples, K. et al. *NXY-059: Neuroprotective effects in rat focal stroke models*. Soc Neurosci Abstr 1999, 25(Part 1): Abstr 235.15.

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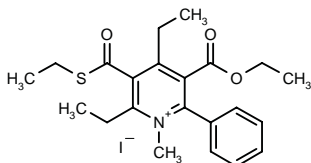
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RESPIRATORY DRUGS

ASTHMA THERAPY

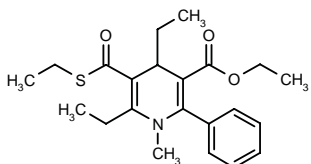
281391

3-(Ethoxycarbonyl)-5-(ethylsulfanylcarbonyl)-4,6-diethyl-1-methyl-2-phenylpyridinium iodide



C22 H28 I N O3 S; Mol wt: 513.4332

ACTION – Adenosine A_3 receptor antagonist with nanomolar affinity for the human A_3 receptor ($K_i = 219$ nM) and high selectivity over rat A_1 and A_{2A} receptors ($K_i = 31,900$ and $11,600$ nM, respectively), as well as over the human A_{2B} receptor ($K_i > 30$ μ M). In an *in vitro* functional test, compound showed pure antagonist activity against agonist (IB-MECA)-induced inhibition of adenylate cyclase in CHO cells ($K_B = 399$ nM). In the presence of rat brain homogenates, compound could be generated through oxidation of the precursor **281961** with similar adenosine A_3 receptor affinity ($K_i = 379$ nM) and selectivity ($K_i = 28.4$ μ M for rat A_1 receptors and > 100 μ M for rat A_2 receptors). Potentially useful as an antiinflammatory, antiasthmatic and antiischemic agent.



281961: C22 H29 N O3 S

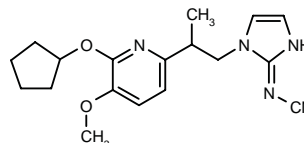
SOURCE – National Institutes of Health, Bethesda, MD (US).

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1. Xie, R. et al. *Selective A_3 adenosine receptor antagonists: Water-soluble 3,5-diacyl-1,2,4-trialkylpyridinium salts and their oxidative generation from dihydropyridine precursors*. J Med Chem 1999, 42(20): 4232.

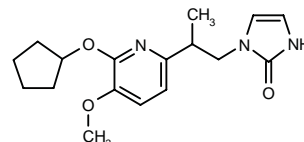
281584

1-[2-(6-Cyclopentyloxy-5-methoxypyridin-2-yl)propyl]-2,3-dihydro-1H-imidazol-2-ylidenecyanamide



C18 H23 N5 O2; Mol wt: 341.4127

ACTION – Agent for the treatment of allergic, atopic and inflammatory disorders with phosphodiesterase type 4 (PDE4; 25% of enzyme activity vs. control when tested against recombinant human mononuclear lymphocyte PDE4B at 0.1 μ M) and cytokine-inhibitory activity, and which is reported to be free of gastrointestinal side effects. Another specifically claimed compound from this series of pyridine derivatives is:



281585: C17 H23 N3 O3

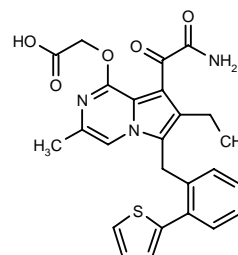
SOURCE – Janssen.

REFERENCES

1. Freyne, E.J.E. et al. (Janssen Pharmaceutica NV) *PDE IV inhibiting pyridine derivs*. WO 9950262.

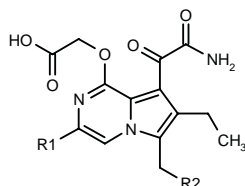
281851

2-[8-(2-Amino-2-oxoacetyl)-7-ethyl-3-methyl-6-[2-(2-thienyl)benzyl]pyrrolo[1,2-a]pyrazin-1-yloxy]acetic acid



C25 H23 N3 O5 S; Mol wt: 477.5387

ACTION – Secretory phospholipase A₂ (sPLA₂) inhibitor (IC₅₀ = 0.005 µM against recombinant human sPLA₂ in a chromogenic assay) for use in the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, bronchial asthma, allergic rhinitis, chronic rheumatism, arteriosclerosis, cerebral hemorrhage, cerebral infarction, inflammatory colitis, psoriasis, heart failure and myocardial infarction. Other exemplified pyrrolo[1,2-*a*]-pyrazines include the following:



Compound	R1	R2	Formula
281852	H	cyclopentyl	C ₁₉ H ₂₃ N ₃ O ₅
281853	Me	2-(Ph-ethynyl)-Ph	C ₂₉ H ₂₅ N ₃ O ₅
281854	Me	2-PhO-Ph	C ₂₇ H ₂₅ N ₃ O ₆
281855	Me	2-(3-thienyl)-Ph	C ₂₅ H ₂₃ N ₃ O ₅ S
281856	Me	2-(5-Me-2-thienyl)-Ph	C ₂₆ H ₂₅ N ₃ O ₅ S
281857	Me	2-(4-Me-Ph)-Ph	C ₂₈ H ₂₇ N ₃ O ₅
281858	Me	2-(PhCH ₂ CH ₂)-Ph	C ₂₉ H ₂₉ N ₃ O ₅
281859	cyclohexyl	Ph	C ₂₆ H ₂₉ N ₃ O ₅
281860	cyclohexyl	2-Ph-Ph	C ₃₂ H ₃₃ N ₃ O ₅

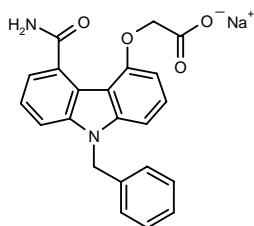
SOURCE – Shionogi.

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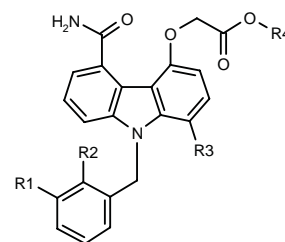
281891

2-(9-Benzyl-5-carbamoyl-9*H*-carbazol-4-yloxy)acetic acid sodium salt

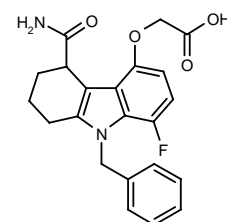


C₂₂ H₁₇ N₂ Na O₄; Mol wt: 396.3763

ACTION – An inhibitor of human nonpancreatic secretory phospholipase A₂ (sPLA₂) with potential in the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis. Other exemplified compounds from this series of substituted carbazoles include the following:



Compound	R1	R2	R3	R4	Formula
281893	H	H	F	H	C ₂₂ H ₁₇ FN ₂ O ₄
281894	F	H	H	H	C ₂₂ H ₁₇ FN ₂ O ₄
281895	Cl	H	H	H	C ₂₂ H ₁₇ ClN ₂ O ₄
281896	CF ₃	H	H	Na	C ₂₃ H ₁₆ F ₃ N ₂ NaO ₄
281897	H	Me	H	Na	C ₂₃ H ₁₉ N ₂ NaO ₄
281898	Me	H	H	Na	C ₂₃ H ₁₉ N ₂ NaO ₄



281892: C₂₂ H₂₁ F N₂ O₄

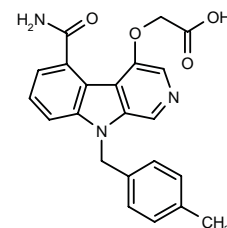
SOURCE – Lilly.

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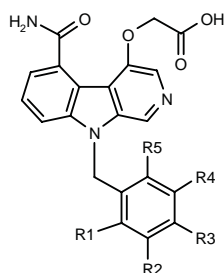
281899

2-[5-Carbamoyl-9-(4-methylbenzyl)-9*H*-pyrido[3,4-*b*]indol-4-yloxy]acetic acid



C₂₂ H₁₉ N₃ O₄; Mol wt: 389.4091

ACTION – An inhibitor of human nonpancreatic secretory phospholipase A₂ (sPLA₂) with potential in the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis. Other substituted tricyclic compounds include the following:



Compound	R1	R2	R3	R4	R5	Formula
281900	H	H	CF ₃	H	H	C ₂₂ H ₁₆ F ₃ N ₃ O ₄
281901	H	H	H	COPh	H	C ₂₈ H ₂₁ N ₃ O ₅
281902	F	H	F	H	F	C ₂₁ H ₁₄ F ₃ N ₃ O ₄
281903	H	H	H	H	F	C ₂₁ H ₁₆ FN ₃ O ₄
281904	F	F	F	F	F	C ₂₁ H ₁₂ F ₅ N ₃ O ₄
281905	H	OMe	OMe	OMe	H	C ₂₄ H ₂₃ N ₃ O ₇
281906	H	F	H	F	H	C ₂₁ H ₁₅ F ₂ N ₃ O ₄

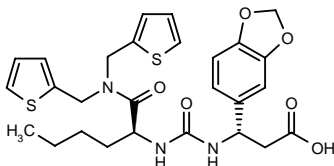
SOURCE – Lilly.

REFERENCES

1. Bach, N.J. et al. (Eli Lilly and Company) *Subst. tricyclics useful in sPLA₂ induced diseases*. EP 950661, JP 99322745.

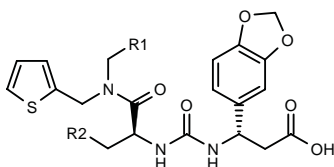
281982

3(S)-(1,3-Benzodioxol-5-yl)-3-[N³-[1(S)-[N,N-bis(2-thienylmethyl)carbamoyl]pentyl]ureido]propionic acid

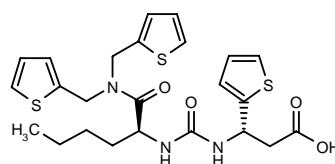


C27 H31 N3 O6 S2; Mol wt: 557.6889

ACTION – An inhibitor of integrin $\alpha_4\beta_1$ binding to, for example, fibronectin and vascular cell adhesion molecule-1 (VCAM-1), potentially useful in the treatment of asthma, atherosclerosis, rheumatoid arthritis, allergy, multiple sclerosis, lupus, inflammatory bowel disease, graft rejection, contact hypersensitivity, type I diabetes and cancer. Other compounds from this series of *N,N*-disubstituted amides include the following:



Compound	R1	R2	Formula
281984	Ph	(CH ₂) ₃ NHCO ₂ CH ₂ Ph	C ₃₇ H ₄₀ N ₄ O ₈ S
281988	2-thienyl	Ph	C ₃₀ H ₂₉ N ₃ O ₆ S ₂
281991	2-thienyl	SCH ₂ Ph	C ₃₁ H ₃₁ N ₃ O ₆ S ₃
281993	3-Pyr	Bu	C ₂₈ H ₃₂ N ₄ O ₆ S
281995	2-thienyl	i-Pr	C ₂₇ H ₃₁ N ₃ O ₆ S ₂
281996	2-thienyl	(CH ₂) ₃ NHCO ₂ CH ₂ Ph	C ₃₈ H ₃₈ N ₄ O ₈ S ₂



281997: C₂₄ H₂₉ N₃ O₄ S₃

SOURCE – Texas Biotechnology.

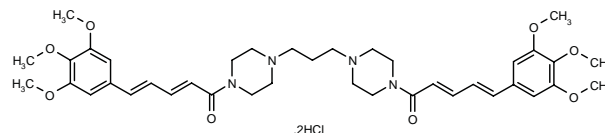
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282101

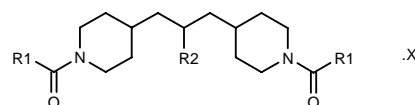
1,3-Bis[4-[5-(3,4,5-trimethoxyphenyl)penta-2(*E*),4(*E*)-dienoyl]piperazin-1-yl]propane dihydrochloride

1,1'-(Propane-1,3-diyl)bis(piperazine-4,1-diyl)bis[5-(3,4,5-trimethoxyphenyl)penta-2(*E*),4(*E*)-dien-1-one] dihydrochloride

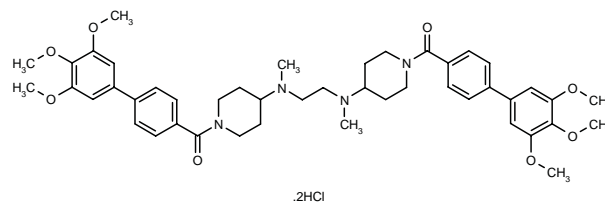


C39 H52 N4 O8 . 2HCl; Mol wt: 777.7816

ACTION – Antiallergic agent with IgE antibody production-inhibitory activity, as demonstrated *in vitro* in lipopolysaccharide- and IL-4-stimulated B-cell fractions from murine spleen cells (100% inhibition at 1 μ M). Other compounds within this series of cyclic amide derivatives include the following:



Compound	R1	R2	X	Formula
282102	5,6-(MeO)2-1,1-(Me)-2-indenyl-CH=CH	H		C ₄₅ H ₅₈ N ₂ O ₆
282103	4-Me-3-[3,4,5-(MeO)3-Ph]-Ph	N(Me) ₂	HCl	C ₄₉ H ₆₃ N ₃ O ₈ .HCl
282104	3,4,5-(MeO)3-Ph-ethynylene-CH=CH	CH ₂ N(Me) ₂	HCl	C ₄₄ H ₅₇ N ₃ O ₈ .HCl



282105: C₄₆ H₅₈ N₄ O₈ . 2HCl

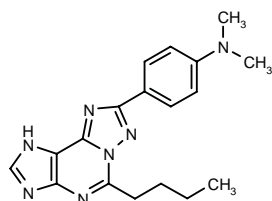
SOURCE – Kowa.

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1. Ishiwata, H. et al. (Kowa Co., Ltd.) *Cyclic amide cpds*. WO 9942446.

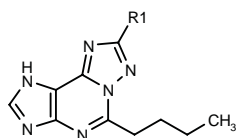
282915

N-[4-(5-Butyl-1*H*-[1,2,4]triazolo[5,1-*f*]purin-8-yl)phenyl]-*N,N*-dimethylamine



C18 H21 N7; Mol wt: 335.4129

ACTION – Antiasthmatic agent with high affinity for adenosine A₃ receptors (IC₅₀ = 1 nM or less) and selectivity relative to A₁ or A₂ receptors (IC₅₀ = 10 μM or greater). Other compounds from this series of triazolopurine derivatives include the following:



Compound	R1	Formula
282916	3,4,5-(MeO)3-Ph	C ₁₉ H ₂₂ N ₆ O ₃
282918	(E)-CH=CHPh	C ₁₈ H ₁₈ N ₆
282919	4-Cl-Ph	C ₁₈ H ₁₅ ClN ₆
282920	4-MeO-Ph	C ₁₇ H ₁₈ N ₆ O
282922	4-PrO-Ph	C ₁₉ H ₂₂ N ₆ O
282923	4-EtO-Ph	C ₁₈ H ₂₀ N ₆ O
282924	4-CF ₃ -Ph	C ₁₇ H ₁₅ F ₃ N ₆
282925	4-(PhCH ₂ NH)-Ph	C ₂₃ H ₂₃ N ₇
282926	2-Naph	C ₂₀ H ₁₈ N ₆

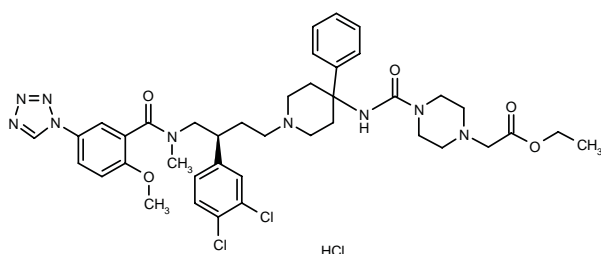
SOURCE – Otsuka.

REFERENCES

1. Okamura, T. et al. (Otsuka Pharmaceutical Co., Ltd.) *Triazolopurine derivs, medicinal compsn. containing the derivs., adenosine A3 receptor compatibilizing agent, and asthmatic remedy*. WO 9951606.

283348

2-[4-[*N*-[1-[3(*S*)-(3,4-Dichlorophenyl)-4-[*N*-[2-methoxy-5-(1*H*-tetrazol-1-yl)benzoyl]-*N*-methylamino]butyl]-4-phenylpiperidin-4-yl]carbamoyl]piperazin-1-yl]acetic acid ethyl ester hydrochloride



C40 H49 Cl₂ N₉ O₅ . HCl; Mol wt: 843.2520

ACTION – Tachykinin, particularly NK₁ and NK₂, receptor antagonist giving IC₅₀ values for NK₁ and NK₂ receptors of 23 and 178 nM, respectively, in binding assays. It is therefore considered to have potential particularly in the treatment of asthma, as well as cough and bronchitis.

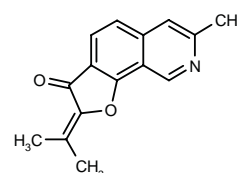
SOURCE – Aventis Pharma.

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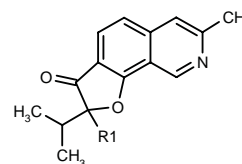
TMC-120B**282029**

7-Methyl-2-(1-methylethylene)furo[3,2-*h*]isoquinolin-3(2*H*)-one



C15 H13 N O₂; Mol wt: 239.2727

ACTION – Potential antiallergic/antiasthmatic agent, an inhibitor of IL-5-mediated prolongation of eosinophil survival (IC₅₀ = 2 μM for inhibition of survival of peritoneal eosinophils from polymixin B-sensitized guinea pigs) extracted from the fermentation broth of the fungus *Aspergillus ustus*. Compound showed no cytotoxicity against human leukemia HL-60 cells at the concentration of 42 μM. Other related compounds isolated from this source are:



Compound	R1	Formula
TMC-120A [282026]	H	C ₁₅ H ₁₅ NO ₂
TMC-120C [282031]	OH	C ₁₅ H ₁₅ NO ₃

SOURCE – Tanabe Seiyaku.

REFERENCES

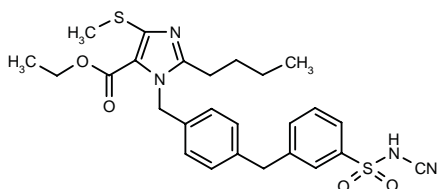
1. Kohno, J. et al. *Production, isolation and biological properties of TMC-120A, B and C, novel inhibitors of eosinophil survival from Aspergillus ustus TC 1118*. J Antibiot 1999, 52(10): 913.

CARDIOVASCULAR DRUGS

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

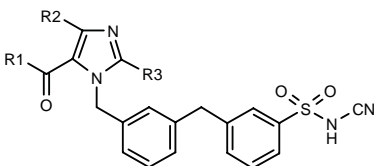
283144

2-Butyl-1-[4-[3-(cyanosulfamoyl)benzyl]benzyl]-4-(methylsulfanyl)-1*H*-imidazole-5-carboxylic acid ethyl ester



C₂₆H₃₀N₄O₄S₂; Mol wt: 526.6790

ACTION – An inhibitor of Na⁺-dependent Cl⁻/HCO₃⁻ exchange (NCBE), as demonstrated in human endothelial cells (about 89% inhibition at a concentration of 10 μM), with cardioprotective and antiproliferative activity. Potentially useful for the treatment or prevention of ischemic disorders, myocardial infarction, angina pectoris, stroke, shock states, respiratory disorders and proliferative disorders. Other compounds from this series of substituted sulfonyl cyanamides include the following:



Compound	R1	R2	R3	Formula
283145	OEt	SMe	Bu	C ₂₆ H ₃₀ N ₄ O ₄ S ₂
283146	H	Cl	Ph	C ₂₅ H ₁₉ ClN ₄ O ₃ S

SOURCE – Aventis Pharma.

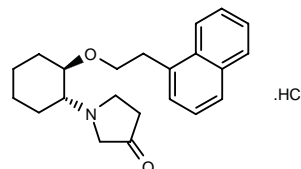
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ANTIARRHYTHMIC DRUGS

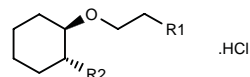
281659

(±)-*trans*-1-[2-[2-(1-Naphthyl)ethoxy]cyclohexyl]pyrrolidin-3-one hydrochloride



C₂₂H₂₇N O₂ . HCl; Mol wt: 373.9212

ACTION – Agent which blocks ion channels and exerts antiarrhythmic, analgesic and anesthetic effects. Compound reduced the arrhythmia score in conscious rats subjected to coronary artery occlusion with an ED₅₀ of 0.43 μmol/kg/min. It appears to act via blockade of cardiac sodium channels and ancillary blockade of cardiac potassium channels, as determined by the increase in P-R, QRS and Q-T intervals when given to rats (ED₂₅ = 15.8, 7.8 and 3.4 μmol/kg i.v., respectively). Other compounds from this series of aminocyclohexyl ether derivatives include the following:



Compound	R1	R2	Formula
281660	2-Naph	4-morpholinyl	C ₂₂ H ₂₉ NO ₂ .HCl
281661	1-Naph	4-morpholinyl	C ₂₂ H ₂₉ NO ₂ .HCl
281662	4-Br-Ph	4-morpholinyl	C ₁₈ H ₂₆ BrNO ₂ .HCl
281663	2-Br-Ph	4-morpholinyl	C ₁₈ H ₂₆ BrNO ₂ .HCl
281664	2,6-(Cl)2-Ph	3-OH-1-pyrrolidinyl	C ₁₈ H ₂₅ Cl ₂ NO ₂ .HCl

SOURCE – Nortran.

REFERENCES

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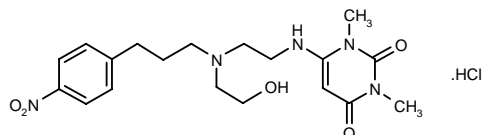
NIFEKALANT HYDROCHLORIDE

Prop INNM

162601

6-[2-[*N*-(2-Hydroxyethyl)-3-(4-nitrophenyl)propylamino]-ethylamino]-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride

MS-551⁺



C₁₉H₂₇N₅O₅ . HCl; Mol wt: 441.9132

ACTION – Potassium channel blocker.

INDICATION – Treatment of arrhythmia.

PRESENTATION – Vials (15 ml), 50 mg.

PROPRIETARY NAME – *Shinbit* (JP).

SOURCES – Manufactured by Mitsui Chemicals; marketed by Mitsui Pharmaceuticals.

RECENT REFERENCES

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- Xue, Y. et al. *MS-551 and KCB-328, two class III drugs aggravated adrenaline-induced arrhythmias.* Br J Pharmacol 1998, 124(8): 1712.
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- Japanese advisory committee recommends approval of class III antiarrhythmic. DailyDrugNews.com (Daily Essentials) 1999, June 8.
- Mitsui Pharmaceuticals pipeline update. DailyDrugNews.com (Daily Essentials) 1997, July 22.
- New type III antiarrhythmic marketed in Japan. DailyDrugNews.com (Daily Essentials) 1999, Nov 2.
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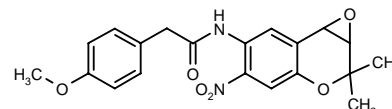
MONOGRAPH – Prous, J. and Castañer, J. *MS-551.* Drugs Fut 1993, 18(3): 0226.

*Drug Data Rep 1990, 012(08): 0623.

HEART FAILURE THERAPY

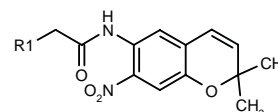
281625

N-(2,2-Dimethyl-5-nitro-1a,7b-dihydro-2*H*-oxireno[*c*][1]-benzopyran-6-yl)-2-(4-methoxyphenyl)acetamide



C₂₀ H₂₀ N₂ O₆; Mol wt: 384.3860

ACTION – Bradycardic agent for the treatment of heart failure shown to reduce heart rate in guinea pig right atrial preparations by 19.6, 60.7, 80.4 and 83.9%, respectively, at concentrations of 10, 30, 100 and 300 μM. Other representative compounds from this series of chromane derivatives include the following:



Compound	R1	Formula
281626	4-MeO-Ph	C ₂₀ H ₂₀ N ₂ O ₅
281627	2-oxo-1-Pip	C ₁₈ H ₂₁ N ₃ O ₅

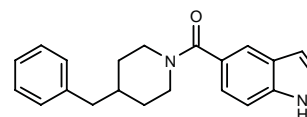
SOURCE – Nissan Chemical.

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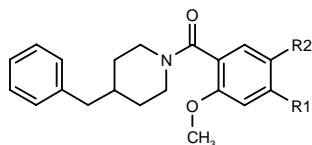
283724

1-(4-Benzylpiperidin-1-yl)-1-(1*H*-indol-5-yl)methanone



C₂₁ H₂₂ N₂ O; Mol wt: 318.4178

ACTION – Selective inhibitor of p38 MAP kinase particularly useful for the treatment of cardiac hypertrophy, ischemia, congestive heart failure, cardiomyopathy and myocarditis, as well as acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, uveitis, inflammatory bowel disease, acute renal failure, head trauma and ischemia/reperfusion injury. Other specifically claimed heterocyclic compounds are:



Compound	R1,R2	Formula
283725	-NHCH=C[CONHCH2CH2N(Me)2]-	C ₂₇ H ₃₄ N ₄ O ₃
283726	-NHCH=N-	C ₂₁ H ₂₃ N ₃ O ₂

SOURCE – Scios.

REFERENCES

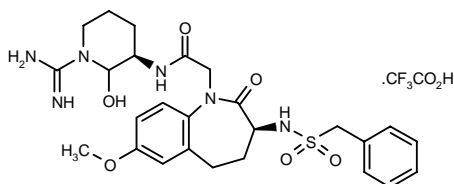
1. Mavunkel, B.J. et al. (Scios Inc.) *Heterocyclic cpds. and methods to treat cardiac failure and other disorders*. WO 9961426.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

280671

N-[1-Amidino-2-hydroxypiperidin-3(*R*)-yl]-3(*S*)-(benzylsulfonamido)-7-methoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-acetamide trifluoroacetate



C₂₆ H₃₄ N₆ O₆ S . C₂ H₃ F₃ O₂; Mol wt: 672.6785

ACTION – Anticoagulant, an inhibitor of blood coagulation factor Xa (IC₅₀ = 7.2 nM) and the prothrombinase complex (IC₅₀ = 34.9 nM) with good to high selectivity relative to thrombin, plasmin (IC₅₀ > 2500 nM) and trypsin (IC₅₀ = 110 nM).

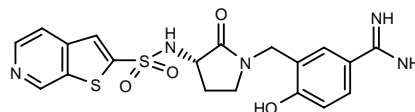
SOURCE – Corvas.

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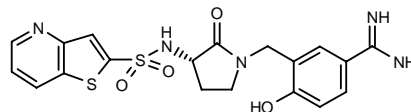
281427

4-Hydroxy-3-[2-oxo-3(*S*)-(thieno[2,3-*c*]pyridin-2-yl)sulfonamido]pyrrolidin-1-ylmethyl]benzamidine



C₁₉ H₁₉ N₅ O₄ S₂; Mol wt: 445.5221

ACTION – Anticoagulant, an inhibitor of factor Xa (K_i = 2 nM) with high selectivity relative to other serine proteases including thrombin, activated protein C, plasmin, trypsin and tissue plasminogen activator (K_i = 2, 18, 6.2, > 2.9 and > 8.7 μM, respectively). In a rat FeCl₂ arterial thrombosis model, compound reduced thrombus mass by 78% and increased the time to occlusion (TTO) by 3.3-fold at a dose of 300 μg/kg by i.v. bolus + 30 μg/kg/min by 75-min infusion. In a canine arteriovenous model of thrombus formation, compound reduced thrombus mass by 91-93% and increased TTO by 3-fold at a dose of 100 μg/kg by i.v. bolus + 10 μg/kg/min by 240-min infusion. Another related compound is:



281428: C₁₉ H₁₉ N₅ O₄ S₂

SOURCE – Aventis Pharma.

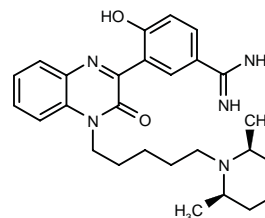
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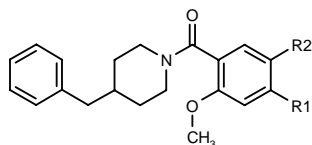
2. Becker, M.R. et al. *Synthesis, SAR and in vivo activity of novel thienopyridine sulfonamide pyrrolidinones as factor Xa inhibitors*. Bioorg Med Chem Lett 1999, 9(18): 2753.

281581

3-[4-[5-[2(*R*),6(*S*)-Dimethylpiperidin-1-yl]pentyl]-3-oxo-3,4-dihydroquinoxalin-2-yl]-4-hydroxybenzamidine



C₂₇ H₃₅ N₅ O₂; Mol wt: 461.6065



Compound	R1,R2	Formula
283725	-NHCH=C[CONHCH2CH2N(Me)2]-	C ₂₇ H ₃₄ N ₄ O ₃
283726	-NHCH=N-	C ₂₁ H ₂₃ N ₃ O ₂

SOURCE – Scios.

REFERENCES

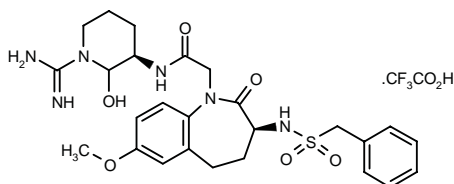
1. Mavunkel, B.J. et al. (Scios Inc.) *Heterocyclic cpds. and methods to treat cardiac failure and other disorders*. WO 9961426.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

280671

N-[1-Amidino-2-hydroxypiperidin-3(*R*)-yl]-3(*S*)-(benzylsulfonamido)-7-methoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-acetamide trifluoroacetate



C₂₆ H₃₄ N₆ O₆ S . C₂ H₃ F₃ O₂; Mol wt: 672.6785

ACTION – Anticoagulant, an inhibitor of blood coagulation factor Xa (IC₅₀ = 7.2 nM) and the prothrombinase complex (IC₅₀ = 34.9 nM) with good to high selectivity relative to thrombin, plasmin (IC₅₀ > 2500 nM) and trypsin (IC₅₀ = 110 nM).

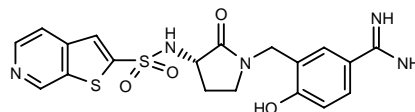
SOURCE – Corvas.

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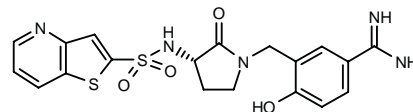
281427

4-Hydroxy-3-[2-oxo-3(*S*)-(thieno[2,3-*c*]pyridin-2-ylsulfonamido)pyrrolidin-1-ylmethyl]benzamidine



C₁₉ H₁₉ N₅ O₄ S₂; Mol wt: 445.5221

ACTION – Anticoagulant, an inhibitor of factor Xa (K_i = 2 nM) with high selectivity relative to other serine proteases including thrombin, activated protein C, plasmin, trypsin and tissue plasminogen activator (K_i = 2, 18, 6.2, > 2.9 and > 8.7 μM, respectively). In a rat FeCl₂ arterial thrombosis model, compound reduced thrombus mass by 78% and increased the time to occlusion (TTO) by 3.3-fold at a dose of 300 μg/kg by i.v. bolus + 30 μg/kg/min by 75-min infusion. In a canine arteriovenous model of thrombus formation, compound reduced thrombus mass by 91-93% and increased TTO by 3-fold at a dose of 100 μg/kg by i.v. bolus + 10 μg/kg/min by 240-min infusion. Another related compound is:



281428: C₁₉ H₁₉ N₅ O₄ S₂

SOURCE – Aventis Pharma.

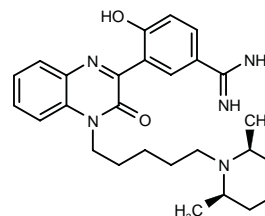
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2. Becker, M.R. et al. *Synthesis, SAR and in vivo activity of novel thienopyridine sulfonamide pyrrolidinones as factor Xa inhibitors*. Bioorg Med Chem Lett 1999, 9(18): 2753.

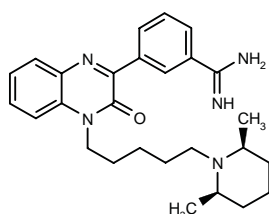
281581

3-[4-[5-[2(*R*),6(*S*)-Dimethylpiperidin-1-yl]pentyl]-3-oxo-3,4-dihydroquinoxalin-2-yl]-4-hydroxybenzamidine



C₂₇ H₃₅ N₅ O₂; Mol wt: 461.6065

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of serine proteases with selectivity for factor Xa (IC_{50} = 0.009 μ M) relative to thrombin (IC_{50} = 7.02 μ M), trypsin (IC_{50} = 2.45 μ M) and factor VIIa (16% inhibition at 100 μ M). In addition, it was shown to inhibit the human prothrombinase (PTase) complex with an IC_{50} value of 0.0015 μ M. It doubled diluted prothrombin time (dPT) at a concentration of 0.05 μ M in human plasma. *In vivo*, it dose-dependently prolonged time to occlusion and reduced net thrombus weight in a rabbit veno-venous shunt model of thrombosis, and at the highest dose tested (480 μ g/kg i.v. + 16 μ g/kg/min i.v.) it prolonged activated partial thromboplastin time (aPTT) and PT by 5- and 3.9-fold, respectively; when tested in a dog electrolytic injury model of thrombosis, it also dose-dependently (2.5-10 μ g/kg/min) prolonged time to occlusion and reduced net thrombus weight, and at the highest dose tested it prolonged aPTT and PT by 1.4- and 1.75-fold, respectively. Another compound from this series of quinoxalinones is:



281582: C₂₇ H₃₅ N₅ O

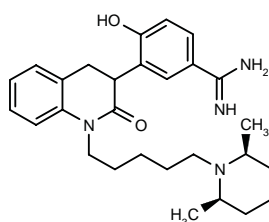
SOURCE – Warner-Lambert.

REFERENCES

1. Dudley, D.A. and Edmunds, J.J. (Warner-Lambert Co.) *Quinoxalinones as serine protease inhibitors such as factor Xa and thrombin*. WO 9950254.

281583

3-[1-[5-[2(*R*),6(*S*)-Dimethylpiperidin-1-yl]pentyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-4-hydroxybenzamide



C₂₈ H₃₈ N₄ O₂; Mol wt: 462.6342

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of serine proteases with selectivity for factor Xa (IC_{50} = 0.02 μ M) over thrombin (IC_{50} = 1.14 μ M) and trypsin (IC_{50} = 0.562 μ M). A representative compound from a series of quinolone derivatives.

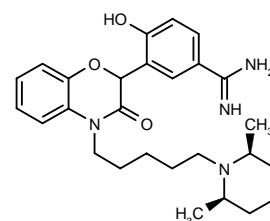
SOURCE – Warner-Lambert.

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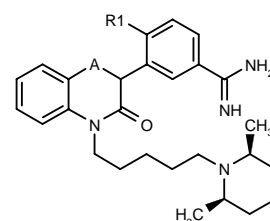
281665

3-[4-[5-[2(*R*),6(*S*)-Dimethylpiperidin-1-yl]pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]-4-hydroxybenzamide



C₂₇ H₃₆ N₄ O₃; Mol wt: 464.6064

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of serine proteases with selectivity for factor Xa (IC_{50} < 0.001 μ M) relative to thrombin (IC_{50} = 1.03 μ M), trypsin (IC_{50} = 0.38 μ M) and factor VIIa (29% inhibition at 100 μ M). In addition, it was shown to inhibit the human prothrombinase complex with an IC_{50} value of 0.00017 μ M. It produced a 5-fold prolongation of diluted prothrombin time (dPT) at concentrations of 0.97, 1.2 and 0.063 μ M in rabbit, dog and human plasma, respectively. A representative compound from a series of benzoxazinones and benzothiazinones, wherein the following are also included:



Compound	R1	A	Isomer	Formula
281666	H	O		C ₂₇ H ₃₆ N ₄ O ₂
281667	H	S		C ₂₇ H ₃₆ N ₄ OS
281668	OH	O	S	C ₂₇ H ₃₆ N ₄ O ₃

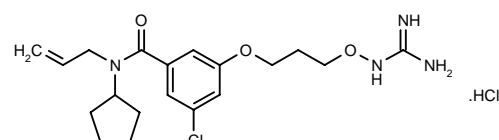
SOURCE – Warner-Lambert.

REFERENCES

1. Berryman, K.A. et al. (Warner-Lambert Co.) *Benzoxazinones/benzothiazinones as serine protease inhibitors*. WO 9950257.

281751

N-Allyl-3-chloro-*N*-cyclopentyl-5-[3-(guanidinoxy)propoxy]benzamide hydrochloride



C₁₉ H₂₇ Cl N₄ O₃ . HCl; Mol wt: 431.3612

ACTION – An inhibitor of proteases, especially trypsin-like serine proteases such as chymotrypsin, trypsin, thrombin, plasmin and factor Xa, a representative compound from a series of benzamide and sulfonamide substituted aminoguanidines and alkoxyguanidines. Certain compounds within the scope of this patent are reported to exhibit antithrombotic activity via direct, selective inhibition of thrombin.

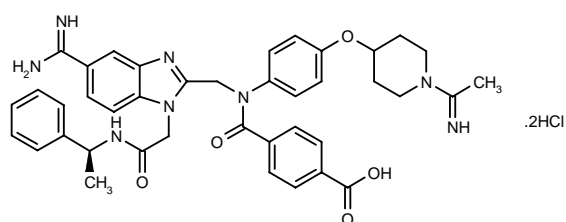
SOURCE – 3-Dimensional Pharmaceuticals.

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1. Soll, R.M. et al. (3-Dimensional Pharmaceuticals, Inc.) *Benzamide and sulfonamide substd. aminoguanidines and alkoxyguanidines as protease inhibitors*. WO 9951571.

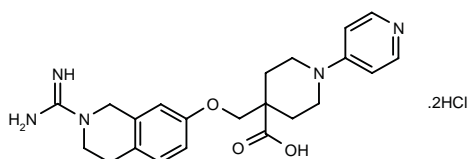
283471

4-[N-[5-Amidino-1-[N-[1(S)-phenylethyl]carbamoylmethyl]-1H-benzimidazol-2-ylmethyl]-N-[4-[1-(ethanimidoyl)piperidin-4-yloxy]phenyl]carbamoyl]benzoic acid dihydrochloride



C40 H42 N8 O5 . 2HCl; Mol wt: 787.7446

ACTION – Anticoagulant that acts by selectively inhibiting factor Xa activity with an IC_{50} of 0.003 μ M, compared to a value of 10 μ M for human thrombin. It doubled the prothrombin time in mouse, rat and human plasma at concentrations of 2, 2 and 0.5 μ M, respectively, and significantly inhibited factor Xa activity *in vivo* in mice and monkeys following both i.v. and p.o. dosing. The compound was also effective in a rat model of thromboplastin-induced thrombocytopenia. Another representative amidine compound is:



283472: C22 H27 N5 O3 . 2HCl

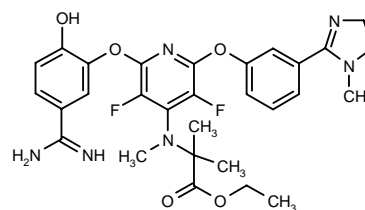
SOURCE – Japan Tobacco.

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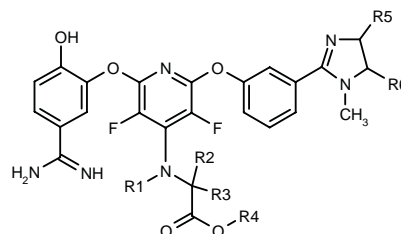
283518

2-[N-[2-(5-Amidino-2-hydroxyphenoxy)-3,5-difluoro-6-[3-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]-N-methylamino]-2-methylpropionic acid ethyl ester



C29 H32 F2 N6 O5; Mol wt: 582.6048

ACTION – Anticoagulant that selectively inhibits factor Xa in *in vitro* assays and proved to be effective as an anticoagulant in thromboplastin-treated rats. Other specifically claimed substituted benzamidine derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Formula
283519	H	H	(CH2)4NHC(=NH)NH2	H	H	H	C ₂₉ H ₃₂ F ₂ N ₆ O ₅
283523	Me	H	Me	Et	H	H	C ₂₈ H ₃₀ F ₂ N ₆ O ₅
283524	Me	Me	Me	H	H	H	C ₂₇ H ₂₈ F ₂ N ₆ O ₅
283529	Me	H	Me	H	H	H	C ₂₆ H ₂₆ F ₂ N ₆ O ₅
283530	H	H	(CH2)4NH2	H	H	H	C ₂₈ H ₃₁ F ₂ N ₇ O ₅
283536	H	H	(CH2)4NHC(=NH)NH2	H	bond		C ₂₉ H ₃₁ F ₂ N ₆ O ₅
283538	H	H	(CH2)4NHC(=NH)Me	H	H	H	C ₃₀ H ₃₄ F ₂ N ₆ O ₅
283539	H	H	(CH2)4NHC(=NH)Me	H	bond		C ₃₀ H ₃₂ F ₂ N ₆ O ₅

SOURCE – Berlex.

REFERENCES

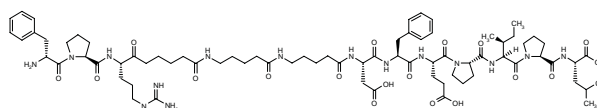
1. Kochanny, M. et al. (Berlex Laboratories, Inc.) *Benzamidine derivs. substd. by amino acid and hydroxy acid derivs. and their use as anti-coagulants*. US 5994375.

BCH-2763*

242185

5-[5-[5-(D-Phenylalanyl-L-propyl-L-arginyl)-pentanamido]pentanamido]pentanoyl-L-aspartyl-L-phenylalanyl-L-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-L-leucine

D-Phenylalanyl-L-propyl-7(S)-amino-10-guanidino-6-oxodecanoyl-5-aminopentanoyl-5-aminopentanoyl-L-aspartyl-L-phenylalanyl-L-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-L-leucine



C75 H113 N15 O18; Mol wt: 1512.8050

ACTION – Anticoagulant, a potent and selective, low-molecular-weight, bifunctional direct thrombin inhibitor ($K_i = 0.11$ nM) that is able to inhibit both free and clot-bound thrombin ($IC_{50} = 9$ and 2166 nM, respectively), unlike heparin. Compound showed superior antithrombotic activity compared to heparin, hirulog, recombinant hirudin, inogatran and argatroban in rat models of arterial and venous thrombosis, without elevating coagulation parameters as much as the other direct thrombin inhibitors, suggesting a favorable safety profile. In a canine electrolytic injury model of venous thrombosis, compound (0.125, 0.25 and 0.75 mg/kg by i.v. bolus, followed by 10, 20 and 60 μ g/kg/min by i.v. infusion, respectively) prolonged the coagulation parameters activated partial thromboplastin time, thrombin time and prothrombin time in a dose-dependent manner and it significantly increased femoral venous blood flow. Potentially useful for the treatment of deep venous thrombosis.

SOURCES – BioChem Pharma; National Research Council of Canada, Montreal, PQ (CA).

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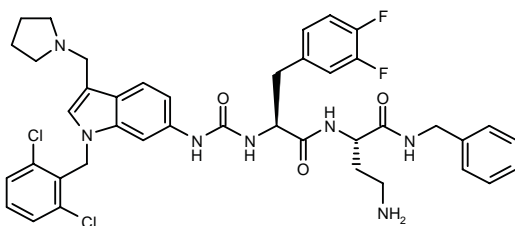
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- Deschenes, I. et al. *Effective use of BCH-2763, a new potent injectable direct thrombin inhibitor, in combination with tissue plasminogen activator (tPA) in a rat arterial thrombolysis model*. FASEB J 1997, 11(3): Abst 1826.
- Deschênes, I. et al. *Effective use of BCH-2763, a new potent injectable direct thrombin inhibitor, in combination with tissue plasminogen activator (tPA) in a rat arterial thrombolysis model*. Thromb Haemost 1998, 80(1): 186.
- Finkle, C. et al. *A new potent direct acting anti-thrombin agent (BCH-2763) is an effective inhibitor of arterial thrombosis in rats*. FASEB J 1996, 10(6): Abst 2395.
- Finkle, C.D. et al. *BCH-2763, a novel potent parenteral thrombin inhibitor, is an effective antithrombotic agent in rodent models of arterial and venous thrombosis - Comparison with heparin, r-hirudin, hirulog, inogatran and argatroban*. Thromb Haemost 1998, 79(2): 431.
- McClanahan, T.B. et al. *Antithrombotic effects of BCH 2763, a new direct thrombin inhibitor, in a canine model of venous thrombosis*. J Thromb Thrombolysis 1999, 7(3): 301.
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- Winocour, P.D. et al. *Effective combined use of new potent injectable direct thrombin inhibitor, BCH-2763, with tissue plasminogen activator (tPA) in a rat arterial thrombolysis model*. Thromb Haemost 1997, (Suppl.): Abst PS-2023.

*Identified compound **242185** Drug Data Rep 1997, 019(02): 0137.

RWJ-56110

279404

4-Amino-N-benzyl-2(S)-[2(S)-[3-[1-(2,6-dichlorobenzyl)-3-(pyrrolidin-1-yl)methyl]-1H-indol-6-yl]ureido]-3-(3,4-difluorophenyl)propionamido]butyramide



C41 H43 Cl2 F2 N7 O3; Mol wt: 790.7387

ACTION – Selective peptidomimetic protease-activated receptor PAR-1 antagonist devoid of PAR-1-agonist and direct thrombin-inhibitory activity. Compound bound to the PAR-1 receptor with high affinity ($IC_{50} = 70$ nM) and inhibited platelet aggregation induced by both SFLLRN and α -thrombin ($IC_{50} = 160$ and 330 nM, respectively) but not by collagen or U-46619 (at up to 50 μ M). It inhibited thrombin-induced Ca^{2+} mobilization in human PAR-1-transfected cells ($IC_{50} = 0.29$ μ M) and in vascular cells including human microvascular endothelial cells ($IC_{50} = 0.13$ μ M), rat aortic smooth muscle cells ($IC_{50} = 0.12$ μ M) and human aortic smooth muscle cell ($IC_{50} = 0.17$ μ M); it also inhibited thrombin-induced proliferation in rat aortic smooth muscle cells with an IC_{50} of 3.5 μ M. Compound had no activity at PAR-2, PAR-3 and PAR-4 receptors. I.v. infusion of compound produced dose-dependent (0.3-3 mg/kg) inhibition of *ex vivo* guinea pig platelet aggregation induced by α -thrombin or SFLLRN. Potentially useful in the treatment of thrombosis and restenosis.

SOURCES – COR Therapeutics; R.W. Johnson.

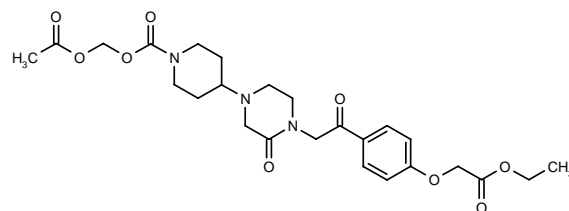
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- Zhang, H.-C. et al. *Novel indole-based peptidomimetics as potent thrombin receptor (PAR-1) antagonists*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 5.

ANTIPLATELET THERAPY

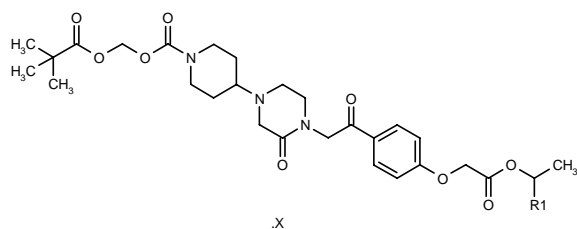
283482

4-[4-[2-[4-(Ethoxycarbonylmethoxy)phenyl]-2-oxoethyl]-3-oxopiperazin-1-yl]piperidine-1-carboxylic acid acetoxymethyl ester



C25 H33 N3 O9; Mol wt: 519.5477

ACTION – Platelet antiaggregatory agent that acts by inhibiting gpIIb/IIIa binding to fibrinogen. It showed good oral bioavailability in rats (36.9%). Other nitrogen-containing heterocyclic compounds include the following:



Compound	R1	X	Formula
283483	H	HCl	C ₂₈ H ₃₉ N ₃ O ₉ ·HCl
283484	Me		C ₂₉ H ₄₁ N ₃ O ₉

SOURCE – Meiji Seika.

REFERENCES

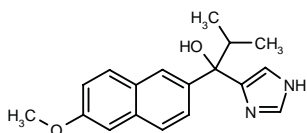
1. Ota, K. et al. (Meiji Seika Kaisha, Ltd.) *Nitrogen-containing heterocyclic cpds. having antiplatelet aggregation effect and medicinal use thereof*. WO 9952894.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

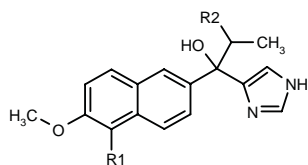
282373

1-(1*H*-Imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-2-methyl-1-propanol



C₁₈ H₂₀ N₂ O₂; Mol wt: 296.3680

ACTION – Steroid C_{17,20}-lyase inhibitor (IC₅₀ = 33 nM in rat testicular microsomes) found to inhibit testosterone biosynthesis in rats at a dose of 50 mg/kg p.o. Potentially useful in the treatment of prostate cancer, prostatic hypertrophy, hirsutism, male pattern baldness, precocious puberty, breast cancer, uterine cancer, uterine myoma, endometriosis, polycystic ovary syndrome, etc. Other exemplified naphthalene derivatives include the following:



Compound	R1	R2	Formula
282374	F	Me	C ₁₈ H ₁₉ FN ₂ O ₂
282375	H	H	C ₁₇ H ₁₈ N ₂ O ₂

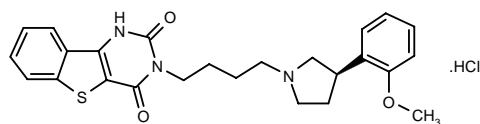
SOURCE – Takeda.

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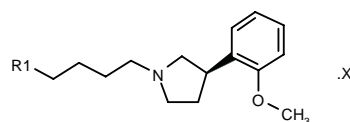
283106

3-[4-[3(*R*)-(2-Methoxyphenyl)pyrrolidin-1-yl]butyl]-benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione hydrochloride



C₂₅ H₂₇ N₃ O₃ S · HCl; Mol wt: 486.0332

ACTION – Agent for the treatment of benign prostatic hyperplasia (BPH) and other urological diseases such as bladder outlet obstruction and neurogenic bladder, as well as gynecological syndromes such as dysmenorrhea, an α₁-adrenoceptor antagonist with K_i values of 0.02, 0.18, 0.62 and 0.03 nM for the α_{1a} (bovine and rat), α_{1b} (hamster) and α_{1d} (rat) subtypes, respectively. Other compounds from this series of 3-phenylpyrrole derivatives include the following:



Compound	R1	X	Formula
283109	2,4-dioxo-1,3-dihydropyrido[2',3':4,5]-thieno-[3,2-d]pyrimidin-3-yl	2HCl	C ₂₄ H ₂₆ N ₄ O ₃ S .2HCl
283111	2,4-dioxo-1,3-dihydropyrido-[3',2':4,5]thieno[3,2-d]pyrimidin-3-yl	2HCl	C ₂₄ H ₂₆ N ₄ O ₃ S .2HCl
283112	8-chloro-2,4-dioxo-1,3-dihydropyrido-[2',3':4,5]thieno[3,2-d]pyrimidin-3-yl	2HCl	C ₂₄ H ₂₅ ClN ₄ O ₃ S .2HCl
283113	1,3-dioxo-2-isindolyl	HCl	C ₂₃ H ₂₆ N ₂ O ₃ .HCl
283114	1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-2-yl	HCl	C ₂₂ H ₂₆ N ₂ O ₄ S .HCl
283115	3,4-dihydro-3-oxo-2H-1,4-benzoxacin-4-yl	HCl	C ₂₃ H ₂₈ N ₂ O ₃ .HCl
283116	2-oxo-1,2,3,4-tetrahydro-1-quinolyl	HCl	C ₂₄ H ₃₀ N ₂ O ₂ .HCl

SOURCE – Abbott.

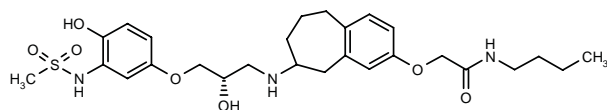
REFERENCES

1. Ehrlich, P.P. et al. (Abbott Laboratories Inc.) *3-Phenylpyrrole α₁-adrenergic cpds*. WO 9957122.

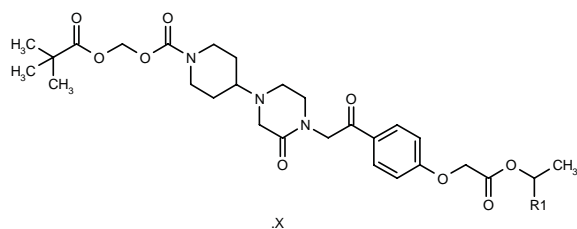
TREATMENT OF URINARY INCONTINENCE

281824

N-Butyl-2-[8-[2(*S*)-hydroxy-3-[4-hydroxy-3-(methanesulfonylamido)phenoxy]propylamino]-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl]oxy]acetamide



C₂₇ H₃₉ N₃ O₇ S; Mol wt: 549.6851



Compound	R1	X	Formula
283483	H	HCl	C ₂₈ H ₃₉ N ₃ O ₉ ·HCl
283484	Me		C ₂₉ H ₄₁ N ₃ O ₉

SOURCE – Meiji Seika.

REFERENCES

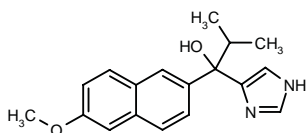
1. Ota, K. et al. (Meiji Seika Kaisha, Ltd.) *Nitrogen-containing heterocyclic cpds. having antiplatelet aggregation effect and medicinal use thereof*. WO 9952894.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

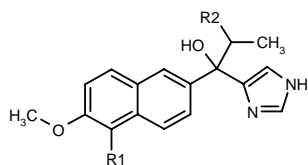
282373

1-(1*H*-Imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-2-methyl-1-propanol



C₁₈ H₂₀ N₂ O₂; Mol wt: 296.3680

ACTION – Steroid C_{17,20}-lyase inhibitor (IC₅₀ = 33 nM in rat testicular microsomes) found to inhibit testosterone biosynthesis in rats at a dose of 50 mg/kg p.o. Potentially useful in the treatment of prostate cancer, prostatic hypertrophy, hirsutism, male pattern baldness, precocious puberty, breast cancer, uterine cancer, uterine myoma, endometriosis, polycystic ovary syndrome, etc. Other exemplified naphthalene derivatives include the following:



Compound	R1	R2	Formula
282374	F	Me	C ₁₈ H ₁₉ FN ₂ O ₂
282375	H	H	C ₁₇ H ₁₈ N ₂ O ₂

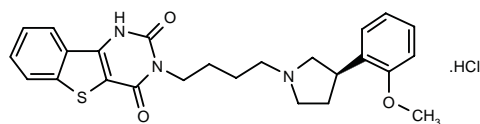
SOURCE – Takeda.

REFERENCES

1. Tasaka, A. et al. (Takeda Chemical Industries, Ltd.) *Naphthalene derivs., their production and use*. WO 9954309.

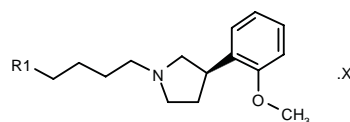
283106

3-[4-[3(*R*)-(2-Methoxyphenyl)pyrrolidin-1-yl]butyl]-benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione hydrochloride



C₂₅ H₂₇ N₃ O₃ S . HCl; Mol wt: 486.0332

ACTION – Agent for the treatment of benign prostatic hyperplasia (BPH) and other urological diseases such as bladder outlet obstruction and neurogenic bladder, as well as gynecological syndromes such as dysmenorrhea, an α₁-adrenoceptor antagonist with K_i values of 0.02, 0.18, 0.62 and 0.03 nM for the α_{1a} (bovine and rat), α_{1b} (hamster) and α_{1d} (rat) subtypes, respectively. Other compounds from this series of 3-phenylpyrrole derivatives include the following:



Compound	R1	X	Formula
283109	2,4-dioxo-1,3-dihydropyrido[2',3':4,5]-thieno-[3,2-d]pyrimidin-3-yl	2HCl	C ₂₄ H ₂₆ N ₄ O ₃ S .2HCl
283111	2,4-dioxo-1,3-dihydropyrido-[3',2':4,5]thieno[3,2-d]pyrimidin-3-yl	2HCl	C ₂₄ H ₂₆ N ₄ O ₃ S .2HCl
283112	8-chloro-2,4-dioxo-1,3-dihydropyrido-[2',3':4,5]thieno[3,2-d]pyrimidin-3-yl	2HCl	C ₂₄ H ₂₅ ClN ₄ O ₃ S .2HCl
283113	1,3-dioxo-2-isindolyl	HCl	C ₂₃ H ₂₆ N ₂ O ₃ .HCl
283114	1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-2-yl	HCl	C ₂₂ H ₂₆ N ₂ O ₄ S .HCl
283115	3,4-dihydro-3-oxo-2H-1,4-benzoxacin-4-yl	HCl	C ₂₃ H ₂₈ N ₂ O ₃ .HCl
283116	2-oxo-1,2,3,4-tetrahydro-1-quinolyl	HCl	C ₂₄ H ₃₀ N ₂ O ₂ .HCl

SOURCE – Abbott.

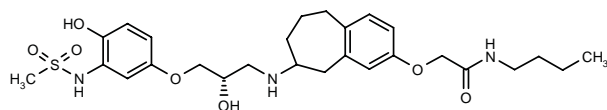
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TREATMENT OF URINARY INCONTINENCE

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N-Butyl-2-[8-[2(*S*)-hydroxy-3-[4-hydroxy-3-(methanesulfonylamido)phenoxy]propylamino]-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl]oxy]acetamide



C₂₇ H₃₉ N₃ O₇ S; Mol wt: 549.6851

ACTION – β_3 -Adrenoceptor agonist with gut-selective sympathomimetic activity, potentially useful for the treatment of urinary incontinence, pollakiuria, ulcers, pancreatitis and lipid disorders. It gave an ED_{50} of 10.8 $\mu\text{g/kg}$ i.v. for inhibiting the increase in intravesical pressure induced by carbachol in anesthetized female dogs.

SOURCE – Fujisawa.

REFERENCES

1. Taniguchi, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Propanolamine derivs.* WO 9951564.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

281586

Helicobacter pylori vaccine comprising an adhesin/CTXA2B chimeric protein consisting of adhesin, an antigenic protein of *H. pylori*, and A2 and B subunits of *Vibrio cholerae* toxin

ACTION – Preventive and therapeutic vaccine for *Helicobacter pylori*-associated diseases such as gastritis, gastric ulcer, duodenal ulcer and gastric cancer comprising a chimeric protein consisting of adhesin of *H. pylori* and A2 and B subunits of *Vibrio cholerae* toxin. The ability to induce an immune response was tested in mice, where p.o. administration of 100 μg of the chimeric protein 3 times at 10-day intervals led to remarkable increases in serum IgG and IgA levels after 18 days, being 2- and 3-fold higher, respectively, than in mice receiving only 100 μg adhesin. In addition, it exhibited a prevention rate of 90% in immunized mice (100 μg p.o. 3 times at 1-week intervals) infected with *H. pylori* Q-35 strain, as compared to a prevention rate of 30% in the animals receiving 100 μg adhesin only. LD_{50} = 4 g/kg p.o. or greater in mice.

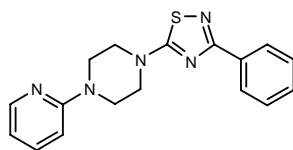
SOURCE – Daewoong.

REFERENCES

1. Kim, B.-O. et al. (Daewoong Pharmaceutical Co., Ltd.) *A preventive and therapeutic vaccine for Helicobacter pylori-associated diseases.* WO 9949890.

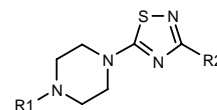
281708

1-(3-Phenyl-1,2,4-thiadiazol-5-yl)-4-(2-pyridinyl)piperazine



C17 H17 N5 S; Mol wt: 323.4223

ACTION – Antiulcer agent, an inhibitor of H^+/K^+ -ATPase proven to inhibit gastric acid secretion *in vitro* in isolated murine gastric glands stimulated with an acid secretagogue (IC_{50} = 4 μM). *In vivo*, it was shown to inhibit gastric acid secretion stimulated by pylorus ligation in rats at 8 and 32 mg/kg p.o. Other compounds from this series of thiadiazole derivatives include the following:



Compound	R1	R2	Formula
281709	2-Pyr	COPh	$C_{18}H_{17}N_5OS$
281710	2-Pyr	3-Cl-PhCO	$C_{18}H_{16}ClN_5OS$
281711	2-Pyr	OMe	$C_{12}H_{15}N_5OS$
281712	2-Pyr	CH(OH)Ph	$C_{18}H_{19}N_5OS$
281713	4-Cl-PhCH(Ph)	COPh	$C_{26}H_{23}ClN_5OS$

SOURCE – Apotex.

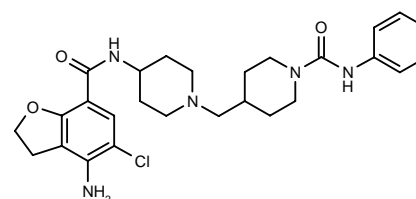
REFERENCES

1. Kharimian, K. et al. (Apotex Inc.) *Thiadiazole cpds. useful as inhibitors of H^+/K^+ ATPase.* WO 9951584.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

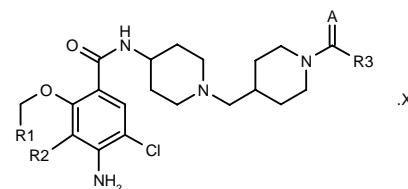
283544

4-[4-(4-Amino-5-chloro-2,3-dihydro-1-benzofuran-7-ylcarboxamido)piperidin-1-ylmethyl]-N-phenylpiperidine-1-carboxamide



C27 H34 Cl N5 O3; Mol wt: 512.0506

ACTION – Gastric prokinetic agent with strong affinity for 5-HT₄ receptors (IC_{50} = 0.36 nM for inhibition of [³H]-GR-113808 binding in guinea pig striatum). It significantly increased fecal weight in mice at a dose of 1 mg/kg p.o. Other exemplified 1-[(1-substituted-4-piperidinyl)methyl]-4-piperidine derivatives include the following:



Compound	R1	R2	R3	A	X	Formula
283546	-CH2-		N(Me)2	S	fumarate	$C_{23}H_{34}ClN_5O_2S$ ·C ₄ H ₄ O ₄
283548	-CH2-		1-pyrrolidinyl	O	fumarate	$C_{25}H_{36}ClN_5O_3$ ·C ₄ H ₄ O ₄
283550	H	H	NHPh	O		$C_{26}H_{34}ClN_5O_3$

ACTION – β_3 -Adrenoceptor agonist with gut-selective sympathomimetic activity, potentially useful for the treatment of urinary incontinence, pollakiuria, ulcers, pancreatitis and lipid disorders. It gave an ED_{50} of 10.8 $\mu\text{g/kg}$ i.v. for inhibiting the increase in intravesical pressure induced by carbachol in anesthetized female dogs.

SOURCE – Fujisawa.

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ANTIULCER DRUGS

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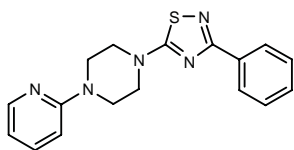
SOURCE – Daewoong.

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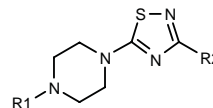
281708

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281709	2-Pyr	COPh	$C_{18}H_{17}N_5OS$
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281711	2-Pyr	OMe	$C_{12}H_{15}N_5OS$
281712	2-Pyr	CH(OH)Ph	$C_{18}H_{19}N_5OS$
281713	4-Cl-PhCH(Ph)	COPh	$C_{26}H_{23}ClN_4OS$

SOURCE – Apotex.

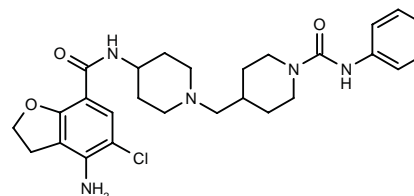
REFERENCES

1. Kharimian, K. et al. (Apotex Inc.) *Thiadiazole cpds. useful as inhibitors of H^+/K^+ ATPase.* WO 9951584.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

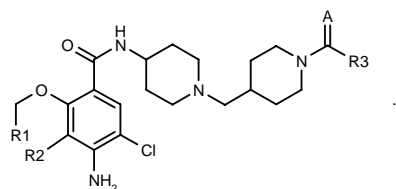
283544

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C27 H34 Cl N5 O3; Mol wt: 512.0506

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Compound	R1	R2	R3	A	X	Formula
283546	-CH2-		N(Me)2	S	fumarate	$C_{23}H_{34}ClN_5O_2S$ $\cdot C_4H_4O_4$
283548	-CH2-		1-pyrrolidinyl	O	fumarate	$C_{25}H_{36}ClN_5O_3$ $\cdot C_4H_4O_4$
283550	H	H	NHPh	O		$C_{26}H_{34}ClN_5O_3$

SOURCE – Dainippon Pharmaceutical.

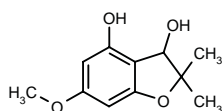
REFERENCES

1. Kato, S. et al. (Dainippon Pharmaceutical Co., Ltd.) 1-[(1-Substd.-4-piperidyl)methyl]-4-piperidine derivs., process for producing the same, medicinal compns. containing the same and intermediates of these cpds. WO 9955674.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

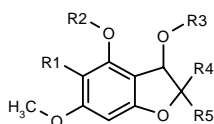
282072

6-Methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-3,4-diol



C11 H14 O4; Mol wt: 210.2276

ACTION – Agent for the treatment of hepatic disorders proven active in a rat model of D-galactosamine-induced hepatic injury, where it reduced AST (GOT) and ALT (GPT) levels in plasma by 46 and 66%, respectively, at a dose of 30 mg/kg/day p.o. x 4 days. Compound was also effective in a murine model of D-galactosamine/lipopolysaccharide-induced liver injury, reducing plasma AST and ALT levels by 66 and 83%, respectively, when given at 2 h and 30 min before D-Gal/LPS at 100 mg/kg p.o. No toxicity was seen in rats at a dose of 300 mg/kg/day p.o. x 4 weeks. Within this series of 3-hydroxy-2,3-dihydrobenzofuran and benzothiophene derivatives, the following are also included:



Compound	R1	R2	R3	R4=R5	Formula
282074	OMe	H	H	Me	C ₁₂ H ₁₆ O ₅
282076	H	Ac	Ac	Me	C ₁₅ H ₁₈ O ₆
282077	OMe	Me	H	H	C ₁₁ H ₁₄ O ₅
282079	OMe	Me	H	Me	C ₁₃ H ₁₈ O ₅

SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Kurokawa, M. et al. (Dainippon Pharmaceutical Co., Ltd.) 3-Hydroxy-2,3-dihydrobenzofuran (or benzothiophene) deris., and therapeutic agents for hepatic disease containing them as effective ingredient. JP 99228563.

ENDOCRINE DRUGS

THYROID DISEASE THERAPY

DOXERCALCIFEROL

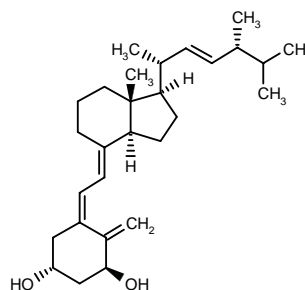
213153

1 α -Hydroxyvitamin D₂

1 α -Hydroxyergocalciferol

9,10-Secoergosta-5(Z),7(E),10(19),22(E)-tetraene-1 α ,3 β -diol

1 α -D₂
One- α D₂
TSA-840



C28 H44 O2; Mol wt: 412.6536

ACTION – Synthetic vitamin D analogue that is metabolically activated *in vivo* to form 1 α ,25-dihydroxyvitamin D₂, a naturally occurring, biologically active form of vitamin D₂.

INDICATION – Reduction of elevated intact parathyroid hormone (iPTH) levels in the management of secondary hyperparathyroidism in patients undergoing chronic renal dialysis.

PRESENTATION – Capsules, 2.5 μ g.

PROPRIETARY NAME – Hectorol (US).

SOURCE – Bone Care International.

REFERENCES

1. Bishop, C.W. et al. (Bone Care International, Inc.) Method of treating prostatic diseases using active vitamin D analogues. US 5763429.
2. Bishop, C.W. et al. (Bone Care International, Inc.) Method of treating prostatic diseases using delayed and/or sustained release vitamin D formulations. US 5795882.
3. DeLuca, H.F. (Wisconsin Alumni Research Foundation) Method for treating calcium imbalance and improving calcium absorption in mammals. US 4225596.
4. DeLuca, H.F. and Kwiecinski, G.G. (Wisconsin Alumni Research Foundation) Method for improving reproductive functions in mammals. WO 9006121.
5. DeLuca, H.F. and Schnoes, H.K. (Wisconsin Alumni Research Foundation) Method for treating metabolic bone disease in mammals. US 4588716.
6. DeLuca, H.F. et al. (Wisconsin Alumni Research Foundation) 1 α -Hydroxyergocalciferol and processes for preparing same. US 3907843.
7. DeLuca, H.F. et al. (Wisconsin Alumni Research Foundation) Method for preparing 1 α -hydroxyvitamin D cpds. US 4554106, WO 8602648.

SOURCE – Dainippon Pharmaceutical.

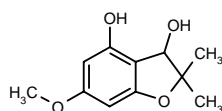
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TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

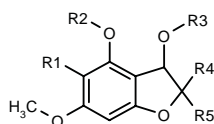
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ENDOCRINE DRUGS

THYROID DISEASE THERAPY

DOXERCALCIFEROL

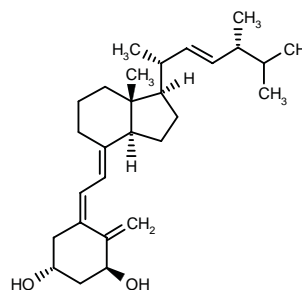
213153

1 α -Hydroxyvitamin D₂

1 α -Hydroxyergocalciferol

9,10-Secoergosta-5(Z),7(E),10(19),22(E)-tetraene-1 α ,3 β -diol

1 α -D₂
One- α D₂
TSA-840



C₂₈ H₄₄ O₂; Mol wt: 412.6536

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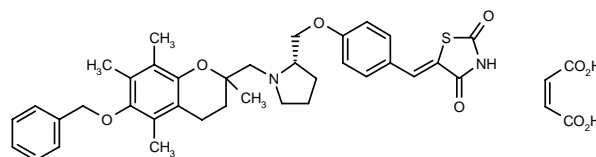
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4. DeLuca, H.F. and Kwiecinski, G.G. (Wisconsin Alumni Research Foundation) Method for improving reproductive functions in mammals. WO 9006121.
5. DeLuca, H.F. and Schnoes, H.K. (Wisconsin Alumni Research Foundation) Method for treating metabolic bone disease in mammals. US 4588716.
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ANTIDIABETIC DRUGS

279994

(Z)-5-[4-[1-(6-Benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-2-ylmethyl)pyrrolidin-2(S)-ylmethoxy]benzylidene]thiazolidine-2,4-dione maleate



C36 H40 N2 O5 S . C4 H4 O4; Mol wt: 728.8586

ACTION – Euglycemic and hypolipidemic agent, an analogue of troglitazone with a superior euglycemic and hypolipidemic profile. Compound, when given orally for 6 days to *db/db* mice at a dose of 30 mg/kg, produced a 48% reduction in plasma glucose and a 47% reduction in triglyceride levels. It did not show high activity in peroxisome proliferator-activated receptor PPAR α and PPAR γ transactivation assays (1.12-fold at 50 μ M and 0.67-fold at 1 μ M, respectively) and appeared to exert its euglycemic and hypolipidemic activity through other mechanisms in addition to binding to PPAR α and PPAR γ . In rats, an oral dose of 100 mg/kg showed a favorable pharmacokinetic profile (C_{\max} = 4.4 μ g/ml, $t_{1/2}$ = 7.12 h).

SOURCE – Dr. Reddy's Research Foundation.

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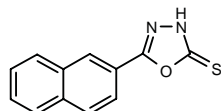
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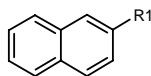
281531

5-(2-Naphthyl)-1,3,4-oxadiazole-2(3H)-thione



C₁₂ H₈ N₂ O S; Mol wt: 228.2742

ACTION – Inhibitor of protein-tyrosine-phosphatases (PTPases) such as PTP1B, PTP α , LAR and TC-PTP with potential in the treatment of diabetes, impaired glucose tolerance, insulin resistance, obesity, cancer, psoriasis, osteoporosis, autoimmune disorders, AIDS, allergic diseases, coagulation disorders, Alzheimer's disease and infectious diseases. Other specifically claimed compounds include the following:



Compound	R1	Formula
281532	5-NH2-1,3,4-oxadiazol-2-yl	C ₁₂ H ₉ N ₃ O
281533	2-oxo-2,3-dihydro-1,3,4-oxadiazol-5-yl	C ₁₂ H ₈ N ₂ O ₂
281535	2-thioxo-2,3-dihydro-1,3,4-oxadiazol-5-yl-CH=CH	C ₁₄ H ₁₀ N ₂ OS
281536	2-oxo-2,3-dihydro-1,3,4-oxadiazol-5-yl-CH=CH	C ₁₄ H ₁₀ N ₂ O ₂
281537	2-(NCNH)-2,3-dihydro-1,3,4-oxadiazol-5-yl	C ₁₃ H ₁₀ N ₄ O

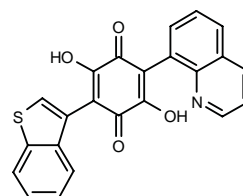
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281797

2-(3-Benzothieryl)-3,6-dihydroxy-5-(8-quinoliny)-1,4-benzoquinone



C₂₃ H₁₃ N O₄ S; Mol wt: 399.4247

ACTION – Antidiabetic agent that is believed to act by virtue of its ability to stimulate insulin receptor tyrosine kinase activity and the activity of phosphoinositide 3-kinase. It therefore acts as an insulin mimetic and insulin-sensitizing agent. Potentially useful in the treatment or prevention of diabetes and obesity, as well as for controlling blood glucose, triglyceride or fatty acid levels.

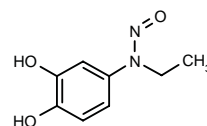
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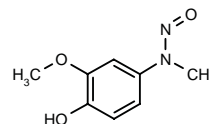
282004

N-(3,4-Dihydroxyphenyl)-N-ethyl-N-nitrosoamine



C₈ H₁₀ N₂ O₃; Mol wt: 182.1780

ACTION – Antidiabetic agent, an inhibitor of protein-tyrosine-phosphatase (IC_{50} = 1.0 μ g/ml). Another compound from this series of N-nitroso-aniline derivatives is:



282005: C₈ H₁₀ N₂ O₃

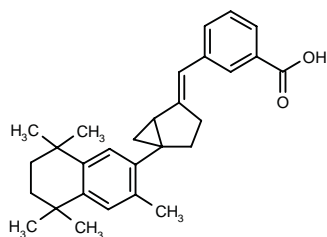
SOURCES – Kaneka; Microbial Chemistry Research Foundation, Tokyo (JP).

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283147

3-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)bicyclo[3.1.0]hex-2-ylidenemethyl]benzoic acid



C29 H34 O2; Mol wt: 414.5856

ACTION – Insulin sensitizer that acts as an agonist at retinoid X receptors (RXR), potentially useful for the treatment of type II diabetes and related disorders, either alone or in combination with peroxisome proliferator-activated receptor (PPAR) agonists.

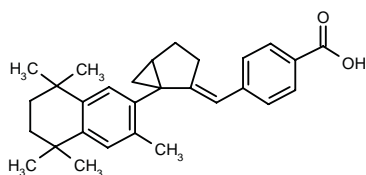
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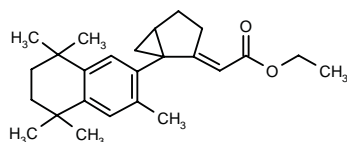
283156

4-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)bicyclo[3.1.0]hex-2-ylidenemethyl]benzoic acid



C29 H34 O2; Mol wt: 414.5856

ACTION – Insulin sensitizer that acts as an agonist at retinoid X receptors (RXR), potentially useful for the treatment of type II diabetes and related disorders, either alone or in combination with peroxisome proliferator-activated receptor (PPAR) agonists. Another exemplified compound is:



283157: C25 H34 O2

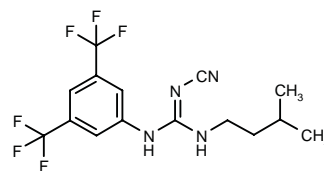
SOURCE – Novo Nordisk.

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283158

N-[3,5-Bis(trifluoromethyl)phenyl]-*N'*-cyano-*N''*-(3-methylbutyl)guanidine



C15 H16 F6 N4; Mol wt: 366.3074

ACTION – Potassium K_{ATP} channel opener giving EC_{50} values for relaxation of phenylephrine-contracted rat aorta rings and for increase in $^{86}Rb^{+}$ efflux from β -cells of 5.6 and 2.6 μM , respectively. Potentially useful for the treatment or prevention of endocrine disorders such as hyperinsulinemia and diabetes.

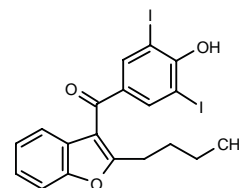
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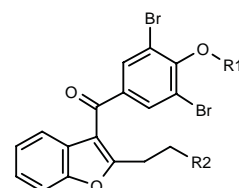
283209

1-(2-Butyl-1-benzofuran-3-yl)-1-(4-hydroxy-3,5-diiodophenyl)methanone



C19 H16 I2 O3; Mol wt: 546.1324

ACTION – Protein-tyrosine-phosphatase (PTPase) inhibitor giving an IC_{50} of 0.19 μM for inhibition of recombinant rat PTP1B and proven to decrease blood glucose and insulin levels by 51.8 and 73.7%, respectively, in diabetic mice. Potentially useful in the treatment of insulin resistance associated with type II diabetes, obesity, glucose intolerance, hypertension and vascular ischemic diseases. Other specifically claimed phenyl oxo-acetic acid derivatives are:



Compound	R1	R2	Formula
283210	CH ₂ CO ₂ H	H	C ₁₉ H ₁₄ Br ₂ O ₅
283211	H	Et	C ₁₉ H ₁₆ Br ₂ O ₃

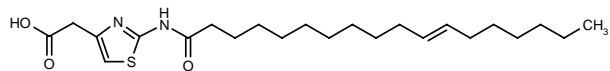
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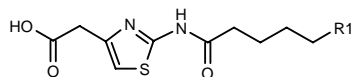
283212

2-[2-[Octadec-11(*E*)-enamido]thiazol-4-yl]acetic acid



C₂₃ H₃₈ N₂ O₃ S; Mol wt: 422.6302

ACTION – Protein-tyrosine-phosphatase (PTPase) inhibitor (IC₅₀ = 0.267 μM against recombinant human PTP1B) potentially useful in the treatment of insulin resistance associated with type II diabetes, obesity, glucose intolerance, hypertension and vascular ischemic diseases. Other specifically claimed 2-(acylaminothiazol-4-yl)acetic acid derivatives are:



Compound	R1	Isomer	Formula
283213	(CH ₂) ₃ CH=CHC ₈ H ₁₇	Z	C ₂₃ H ₃₈ N ₂ O ₃ S
283214	(CH ₂) ₃ CH=CHC ₈ H ₁₇	E	C ₂₃ H ₃₈ N ₂ O ₃ S
283215	(CH ₂) ₃ -ethynylene-C ₈ H ₁₇		C ₂₃ H ₃₆ N ₂ O ₃ S
283216	CH=CHC ₁₁ H ₂₃	Z	C ₂₃ H ₃₈ N ₂ O ₃ S
283217	(CH ₂) ₃ CH=CHC ₆ H ₁₃	Z	C ₂₃ H ₃₈ N ₂ O ₃ S
283218	(CH ₂) ₃ CH=CHC ₆ H ₁₃	E	C ₂₃ H ₃₈ N ₂ O ₃ S
283219	(CH ₂) ₃ (CH=CHCH ₂) ₃ Me	(all Z)	C ₂₃ H ₃₄ N ₂ O ₃ S

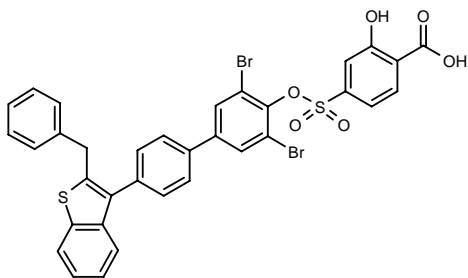
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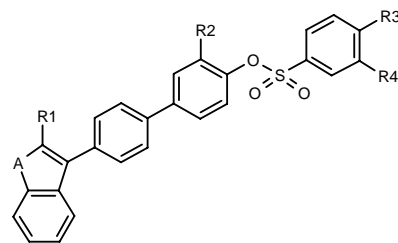
283227

4-[4'-(2-Benzylbenzo[*b*]thiophen-3-yl)-3,5-dibromobiphenyl-4-yloxysulfonyl]-2-hydroxybenzoic acid

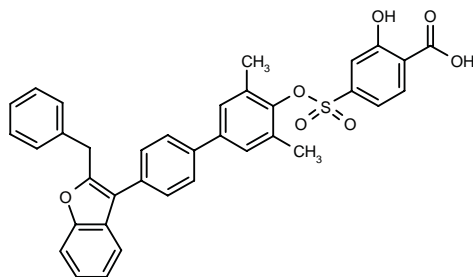


C₃₄ H₂₂ Br₂ O₆ S₂; Mol wt: 750.4818

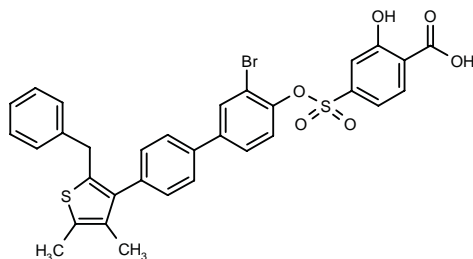
ACTION – Protein-tyrosine-phosphatase (PTPase) inhibitor (IC₅₀ = 0.030 μM against recombinant human PTP1B) proven to decrease blood glucose levels by 24.6% at 25 mg/kg/day by gavage in *ob/ob* mice. Potentially useful in the treatment of insulin resistance associated with type II diabetes, obesity, glucose intolerance, hypertension and vascular ischemic diseases. Other specifically claimed biphenyl sulfonyl aryl-carboxylic acids are:



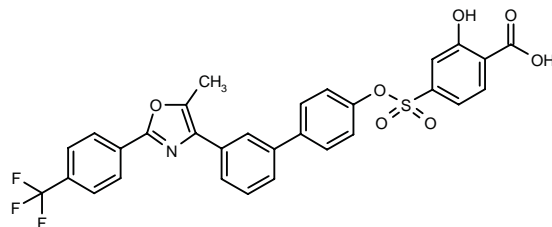
Compound	R1	R2	R3	R4	A	Formula
283228	CH ₂ Ph	H	CO ₂ H	OH	O	C ₃₄ H ₂₄ O ₇ S
283230	CH ₂ Ph	H	OH	CO ₂ H	O	C ₃₄ H ₂₄ O ₇ S
283232	CH ₂ Ph	H	CO ₂ H	H	O	C ₃₄ H ₂₄ O ₆ S
283234	CH ₂ Ph	H	H	CO ₂ H	O	C ₃₄ H ₂₄ O ₆ S
283236	CH ₂ Ph	H	CO ₂ H	OH	S	C ₃₄ H ₂₄ O ₆ S ₂
283237	CH ₂ Ph	Br	CO ₂ H	OH	S	C ₃₄ H ₂₃ BrO ₆ S ₂
283240	COPh	NO ₂	CO ₂ H	OH	O	C ₃₄ H ₂₁ NO ₁₀ S
283241	CH ₂ Ph	Br	CO ₂ H	OH	O	C ₃₄ H ₂₃ BrO ₇ S
283242	COPh	cyclopentyl	CO ₂ H	OH	O	C ₃₈ H ₃₀ O ₆ S
283244	H	H	CO ₂ H	OH	O	C ₂₇ H ₁₈ O ₇ S



283239: C₃₆ H₂₈ O₇ S



283243: C₃₂ H₂₅ Br O₆ S₂



283245: C₃₀ H₂₀ F₃ N O₇ S

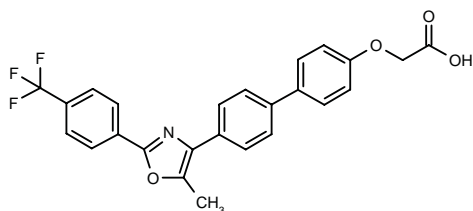
SOURCE – American Home Products.

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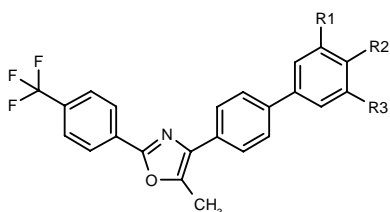
283247

2-[4'-[2-(4-Trifluoromethylphenyl)-5-methyloxazol-4-yl]biphenyl-4-yloxy]acetic acid

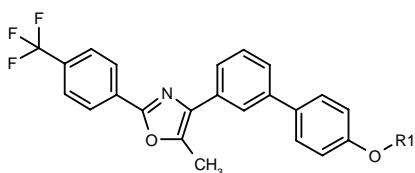


C25 H18 F3 N O4; Mol wt: 453.4142

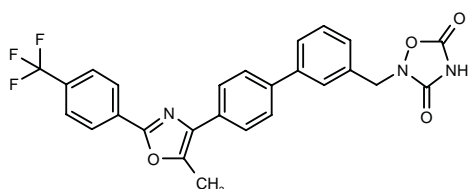
ACTION – Protein-tyrosine-phosphatase (PTPase) inhibitor ($IC_{50} = 0.85 \mu M$ against recombinant human PTP1B) proven to decrease blood glucose levels by 40% at 100 mg/kg/day by gavage in *ob/ob* mice. Potentially useful in the treatment of insulin resistance associated with type II diabetes, obesity, glucose intolerance, hypertension and vascular ischemic diseases. Other specifically claimed oxazole-aryl-carboxylic acids are:



Compound	R1	R2	R3	Formula
283248	H	OMe	H	C ₂₄ H ₁₈ F ₃ NO ₂
283250	H	OH	H	C ₂₃ H ₁₆ F ₃ NO ₂
283254	H	OCH(CH ₂ Ph)CO ₂ H	H	C ₃₂ H ₂₄ F ₃ NO ₄
283257	Br	OH	Br	C ₂₃ H ₁₄ Br ₂ F ₃ NO ₂
283258	Br	OCH ₂ CO ₂ H	Br	C ₂₅ H ₁₆ Br ₂ F ₃ NO ₄
283259	Br	OCH(CH ₂ Ph)-CO ₂ Me	Br	C ₃₃ H ₂₄ Br ₂ F ₃ NO ₄
283260	Br	OCH(CH ₂ Ph)CO ₂ H	Br	C ₃₂ H ₂₂ Br ₂ F ₃ NO ₄
283261	H	3,5-dioxo-1,2,4-oxadiazolidin-2-yl-CH ₂	H	C ₂₆ H ₁₈ F ₃ N ₃ O ₄
283263	H	5-tetrazolyl-CH ₂ O	H	C ₂₈ H ₁₈ F ₃ N ₅ O ₂



Compound	R1	Formula
283249	Me	C ₂₄ H ₁₈ F ₃ NO ₂
283251	H	C ₂₃ H ₁₆ F ₃ NO ₂
283252	CH ₂ CO ₂ H	C ₂₅ H ₁₈ F ₃ NO ₄
283256	CH(CH ₂ Ph)CO ₂ H	C ₃₂ H ₂₄ F ₃ NO ₄



283262: C₂₆ H₁₈ F₃ N₃ O₄

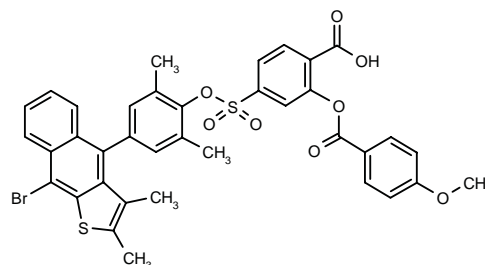
SOURCE – American Home Products.

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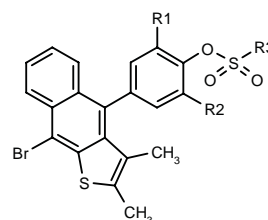
283316

4-[4-(9-Bromo-2,3-dimethylnaphtho[2,3-*b*]thiophen-4-yl)-2,6-dimethylphenoxysulfonyl]-2-(4-methoxybenzoyloxy)-benzoic acid



C37 H29 Br O8 S2; Mol wt: 745.6641

ACTION – Protein-tyrosine-phosphatase (PTPase) inhibitor ($IC_{50} = 0.015 \mu M$ against recombinant human PTP1B) with potential in the treatment of metabolic disorders related to insulin resistance or hyperglycemia, i.e., obesity, glucose intolerance, diabetes mellitus, hypertension and vascular ischemic diseases, more particularly type II diabetes. Other exemplified naphtho[2,3-*b*]hetero-4-yl derivatives include the following:



Compound	R1	R2	R3	Formula
283317	cyclopentyl	H	3-OH-4-CO ₂ H-Ph	C ₃₂ H ₂₇ BrO ₆ S ₂
283318	Me	Me	3-(PhCOO)-4-CO ₂ H-Ph	C ₃₆ H ₂₇ BrO ₇ S ₂
283319	cyclopentyl	H	3-OH-4-CO ₂ H-2-thienyl	C ₃₀ H ₂₅ BrO ₆ S ₃
283320	Me	Me	3-(4-CN-PhCOO)-4-CO ₂ H-Ph	C ₃₇ H ₂₅ BrNO ₇ S ₂

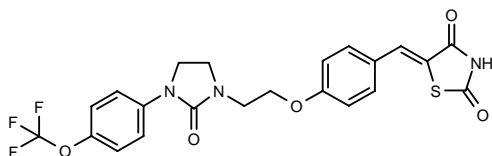
SOURCE – American Home Products.

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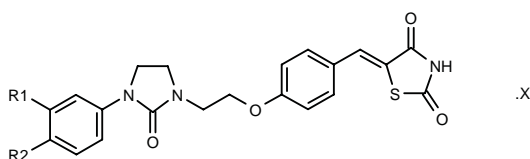
283323

(Z)-5-[4-[2-[3-[4-(Trifluoromethoxy)phenyl]-2-oxoimidazolidin-1-yl]ethoxy]benzylidene]thiazolidine-2,4-dione

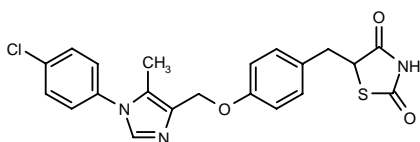


C₂₂ H₁₈ F₃ N₃ O₅ S; Mol wt: 493.4602

ACTION – Antidiabetic agent with blood sugar- and lipid-lowering effects, found to significantly reduce blood sugar levels (53%) following oral administration to KKA^y mice. Compound showed good absorption and a long duration of activity. Other exemplified thiazolidinedione derivatives are:



Compound	R1	R2	X	Formula
283324	H	CF ₃		C ₂₂ H ₁₈ F ₃ N ₃ O ₅ S
283326	H	Cl	hydrate	C ₂₁ H ₁₈ ClN ₃ O ₅ S·H ₂ O
283327	F	F	hydrate	C ₂₁ H ₁₇ F ₂ N ₃ O ₅ S·H ₂ O



283328: C₂₁ H₁₈ Cl N₃ O₃ S

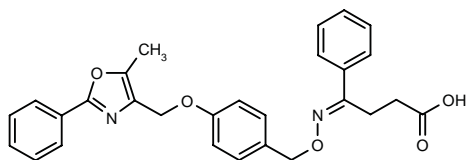
SOURCE – Taiho.

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283345

4-[(E)-4-(5-Methyl-2-phenyloxazol-4-ylmethoxy)benzyl-oxyimino]-4-phenylbutyric acid



C₂₈ H₂₆ N₂ O₅; Mol wt: 470.5224

ACTION – Hypoglycemic and hypolipidemic agent with excellent peroxisome proliferator-activated receptor PPAR γ -agonist activity (EC₅₀ = 0.024 μ M in a PPAR γ -PPAR α heterodimer transactivation assay). It was also shown to significantly reduce blood glucose and triglyceride levels in KKA^y mice, producing respective reductions of 42 and 61% at a concentration of 0.01% in the diet. Potentially useful for improving insulin resistance and for treating or preventing diabetes mellitus.

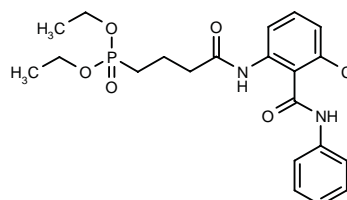
SOURCE – Takeda.

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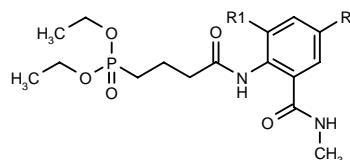
283479

3-[N-[3-Chloro-2-(N-phenylcarbamoyl)phenyl]carbamoyl-propyl]phosphonic acid diethyl ester



C₂₁ H₂₆ Cl N₂ O₅ P; Mol wt: 452.8724

ACTION – Hypoglycemic agent with potential in the treatment of diabetes; it displayed significant blood glucose-lowering effects in dexamethasone-treated rats at a dose of 100 mg/kg/day p.o. for 4 days. Other exemplified phosphonic diester derivatives are:



Compound	R1	R2	Formula
283480	Me	H	C ₁₇ H ₂₇ N ₂ O ₅ P
283481	H	NO ₂	C ₁₈ H ₂₄ N ₃ O ₇ P

SOURCE – Otsuka.

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1. Sakai, Y. et al. (Otsuka Pharmaceutical Co., Ltd.) *Phosphonic diester derivs.* JP 99302291, WO 9955713.

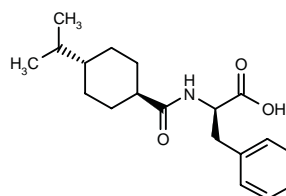
NATEGLINIDE

Prop INN

127137

(-)-N-(trans-4-Isopropylcyclohexyl-1-carbonyl)-D-phenyl-alanine

A-4166⁺
AY-4166
DJN-608
SDZ-DJN-608
YM-026



C₁₉ H₂₇ N O₃; Mol wt: 317.4320

ACTION – Fast-acting insulin segretagogue.

INDICATION – For the improvement of postprandial glucose control in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II diabetes).

PRESENTATION – Tablets, 30 and 90 mg.

PROPRIETARY NAMES – *Fastic* (Nippon Hoechst Marion Roussel; JP) *Starsis* (Yamanouchi; JP).

SOURCES – Ajinomoto; marketed by Nippon Hoechst Marion Roussel; codeveloped and comarketed by Yamanouchi.

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*Drug Data Rep 1989, 011(06): 0474.

RECOMBINANT HUMAN INSULIN

255451

Recombinant human insulin

HR-1799

ACTION – Recombinant human insulin.

INDICATION – Treatment of type I and type II diabetes mellitus.

PRESENTATION – *Insuman rapid* (100% regular insulin), 40 and 100 IU/ml; *Insuman Basal* (100% NPH), 40 and 100 IU/ml; *Insuman Comb 50* (50% regular insulin/50% NPH), 40 and 100 IU/ml; *Insuman Comb 30* (30% regular insulin/70% NPH), 100 IU/ml only; *Insuman Comb 25* (25% regular insulin/75% NPH), 40 and 100 IU/ml; *Insuman Comb 15* (15% regular insulin/85% NPH), 40 and 100 IU/ml; *Insuman Infusat* (100% regular insulin and Genapol as a stabilizing agent for use in insulin pumps), 100 IU/ml only.

PROPRIETARY NAME – *Insuman* (DE).

SOURCE – Aventis Pharma.

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3. *Sixty new products in the forecasted Aventis pipeline*. DailyDrugNews.com (Daily Essentials) 1998, Dec 4.
4. *Insuman® - Human insulin in Hoechst form*. Insuman Web site.

WF-00144

283715

ACTION – Andibabetic agent produced by fermentation of a strain of the genus *Phoma*, proven to inhibit gluconeogenesis in rat hepatocytes with an IC_{50} value of 0.08 µg/ml.

SOURCE – Fujisawa.

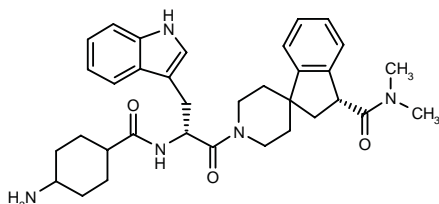
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TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

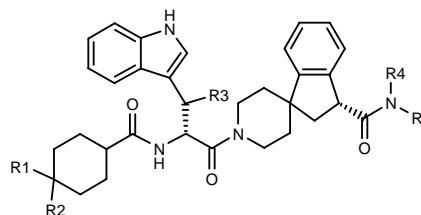
281498

1'-[2(*R*)-(4-Aminocyclohexylcarboxamido)-3-(1*H*-indol-3-yl)propionyl]-*N,N*-dimethylspiro[indane-1,4'-piperidine]-3(*R*)-carboxamide

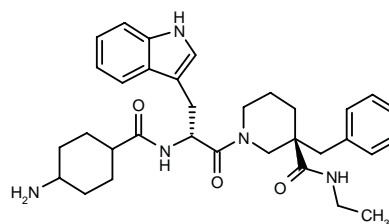


C34 H43 N5 O3; Mol wt: 569.7457

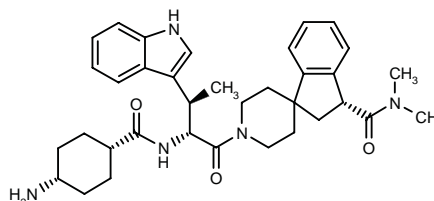
ACTION – Growth hormone (GH) release-promoting agent for the treatment of disorders characterized by a deficiency in GH secretion such as short stature in GH-deficient children, and for the treatment of disorders which are improved by the anabolic effects of GH, particularly osteoporosis. Within this series of piperidine derivatives, the following compounds are also specifically claimed:



Compound	R1	R2	R3	R4	R5	Formula
281499	H	NH2	Me	Me	Me	C ₃₅ H ₄₅ N ₅ O ₃
281501	H	N(Me) ₂	Me	Me	Me	C ₃₇ H ₄₉ N ₅ O ₃
281502	Me	NH2	Me	Me	Me	C ₃₆ H ₄₇ N ₅ O ₃
281503	H	NH2	H	Pr	H	C ₃₅ H ₄₅ N ₅ O ₃



281504: C33 H43 N5 O3



281500: C35 H45 N5 O3

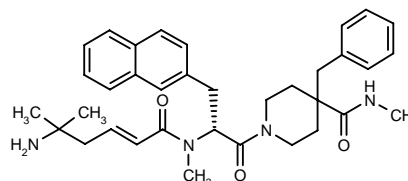
SOURCE – Merck & Co.

REFERENCES

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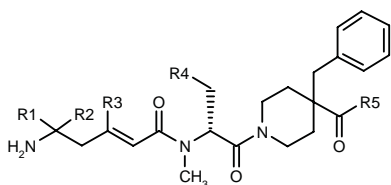
283281

1-[2(*R*)-[5-Amino-5,*N*-dimethyl-2(*E*)-hexenamido]-3-(naphthalen-2-yl)propionyl]-4-benzyl-*N*-methylpiperidine-4-carboxamide

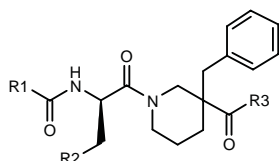


C35 H44 N4 O3; Mol wt: 568.7576

ACTION – Growth hormone secretagogue that has no or virtually no side effects, i.e., release of luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), ACTH, vasopressin, oxytocin, cortisol and/or prolactin, and shows good oral bioavailability. Potentially useful in the treatment of disorders related to growth hormone deficiency. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	R5	Formula
283282	Me	Me	Me	2-Naph	NHMe	C ₃₆ H ₄₆ N ₄ O ₃
283284	-(CH ₂) ₃ -		H	4-Ph-Ph	NHMe	C ₃₈ H ₄₆ N ₄ O ₃
283287	Me	Me	H	2-Naph	OEt	C ₃₆ H ₄₅ N ₃ O ₄
283289	Me	Me	H	2-Naph	NH-N(Me) ₂	C ₃₆ H ₄₇ N ₅ O ₃



Compound	R1	R2	R3	Isomer	Formula
283285	C(Me) ₂ NH ₂	3-indolyl	NHN(Me) ₂	R	C ₃₀ H ₄₀ N ₆ O ₃
283288	CH=CHCH ₂ -C(Me) ₂ NH ₂	3-indolyl	OEt	S	C ₃₃ H ₄₂ N ₄ O ₄
283290	CH=CHCH ₂ -C(Me) ₂ NH ₂	OCH ₂ Ph	NHN(Me) ₂	S	C ₃₂ H ₄₅ N ₅ O ₄
283291	C(Me) ₂ NH ₂	4-Ph-Ph	NHN(Me) ₂		C ₃₄ H ₄₃ N ₅ O ₃
283292	C(Me) ₂ NH ₂	3-indolyl	NHN(Me) ₂		C ₃₀ H ₄₀ N ₆ O ₃

SOURCE – Novo Nordisk.

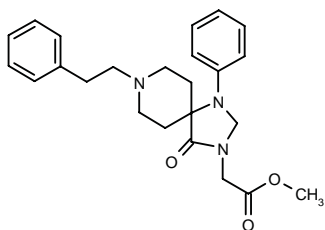
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TREATMENT OF GYNECOLOGICAL DISORDERS

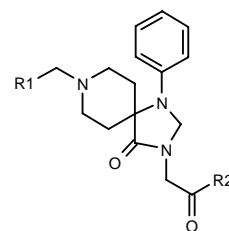
283637

2-[4-Oxo-1-phenyl-8-(2-phenylethyl)-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester



C24 H29 N3 O3; Mol wt: 407.5111

ACTION – Nociceptin (ORL1) receptor ligand (IC₅₀ < 1 μM) potentially useful for the treatment of peripheral vasomotor disturbances, in particular hot flushes. Compound is also claimed to be useful in the treatment of migraine, non-insulin-dependent diabetes mellitus, sepsis, inflammation, incontinence, and/or for alleviating the symptoms of drug withdrawal. Other specifically claimed 1,3,8-triazaspiro[4.5]decanones are:



Compound	R1	R2	Formula
283638	6,7-(MeO)2-2-oxo-2H-1-benzopyran-4-yl	OMe	C ₂₈ H ₃₁ N ₃ O ₇
283639	1-Naph	NHCH ₂ CH ₂ -NHC(=NH)NH ₂	C ₂₉ H ₃₅ N ₇ O ₂
283640	1-Naph	NH(CH ₂) ₃ NH ₂	C ₂₉ H ₃₅ N ₅ O ₂
283641	1-Naph	NHCH ₂ CONH ₂	C ₂₈ H ₃₁ N ₅ O ₃
283642	3,4-(Cl)2-Ph	OMe	C ₂₃ H ₂₅ Cl ₂ N ₃ O ₃

SOURCE – Novo Nordisk.

REFERENCES

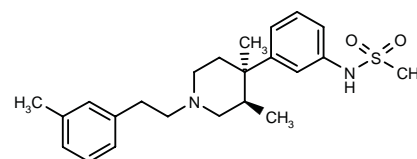
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DERMATOLOGIC DRUGS

TREATMENT FOR ALLERGIC SKIN DISORDERS

283346

(±)-*cis*-N-[3-[3,4-Dimethyl-1-[2-(3-methylphenyl)ethyl]piperidin-4-yl]phenyl]methanesulfonamide



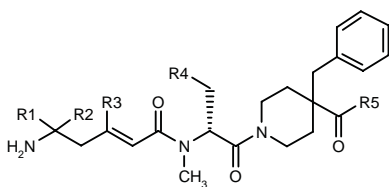
C23 H32 N2 O2 S; Mol wt: 400.5838

ACTION – Antipruritic agent found effective in a rat model of hindleg scratching induced by the known pruritogenic agent 5-methoxytryptamine hydrochloride. Potentially useful for the treatment of pruritic dermatoses including allergic dermatitis and atopy.

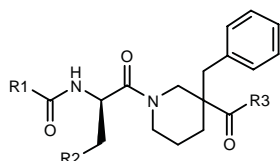
SOURCE – Pfizer.

REFERENCES

- Armer, R.E. et al. (Pfizer Inc.;Pfizer Ltd.) *Novel 4-phenylpiperidines for the treatment of pruritic dermatoses*. WO 9959971.



Compound	R1	R2	R3	R4	R5	Formula
283282	Me	Me	Me	2-Naph	NHMe	C ₃₆ H ₄₆ N ₄ O ₃
283284	-(CH ₂) ₃ -		H	4-Ph-Ph	NHMe	C ₃₈ H ₄₆ N ₄ O ₃
283287	Me	Me	H	2-Naph	OEt	C ₃₆ H ₄₅ N ₃ O ₄
283289	Me	Me	H	2-Naph	NH-N(Me) ₂	C ₃₆ H ₄₇ N ₅ O ₃



Compound	R1	R2	R3	Isomer	Formula
283285	C(Me) ₂ NH ₂	3-indolyl	NHN(Me) ₂	R	C ₃₀ H ₄₀ N ₆ O ₃
283288	CH=CHCH ₂ -C(Me) ₂ NH ₂	3-indolyl	OEt	S	C ₃₃ H ₄₂ N ₄ O ₄
283290	CH=CHCH ₂ -C(Me) ₂ NH ₂	OCH ₂ Ph	NHN(Me) ₂	S	C ₃₂ H ₄₅ N ₅ O ₄
283291	C(Me) ₂ NH ₂	4-Ph-Ph	NHN(Me) ₂		C ₃₄ H ₄₃ N ₅ O ₃
283292	C(Me) ₂ NH ₂	3-indolyl	NHN(Me) ₂		C ₃₀ H ₄₀ N ₆ O ₃

SOURCE – Novo Nordisk.

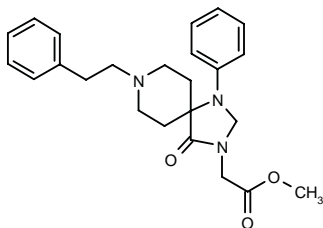
REFERENCES

- Hansen, T.K. and Ankersen, M. (Novo Nordisk A/S) *Cpds. with growth hormone releasing properties*. WO 9958501.

TREATMENT OF GYNECOLOGICAL DISORDERS

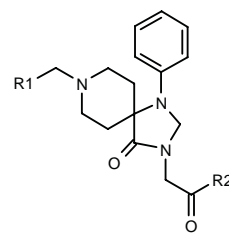
283637

2-[4-Oxo-1-phenyl-8-(2-phenylethyl)-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester



C₂₄ H₂₉ N₃ O₃; Mol wt: 407.5111

ACTION – Nociceptin (ORL1) receptor ligand (IC₅₀ < 1 μM) potentially useful for the treatment of peripheral vasomotor disturbances, in particular hot flushes. Compound is also claimed to be useful in the treatment of migraine, non-insulin-dependent diabetes mellitus, sepsis, inflammation, incontinence, and/or for alleviating the symptoms of drug withdrawal. Other specifically claimed 1,3,8-triazaspiro[4.5]decanones are:



Compound	R1	R2	Formula
283638	6,7-(MeO)2-2-oxo-2H-1-benzopyran-4-yl	OMe	C ₂₈ H ₃₁ N ₃ O ₇
283639	1-Naph	NHCH ₂ CH ₂ -NHC(=NH)NH ₂	C ₂₉ H ₃₅ N ₇ O ₂
283640	1-Naph	NH(CH ₂) ₃ NH ₂	C ₂₉ H ₃₅ N ₅ O ₂
283641	1-Naph	NHCH ₂ CONH ₂	C ₂₈ H ₃₁ N ₅ O ₃
283642	3,4-(Cl)2-Ph	OMe	C ₂₃ H ₂₅ Cl ₂ N ₃ O ₃

SOURCE – Novo Nordisk.

REFERENCES

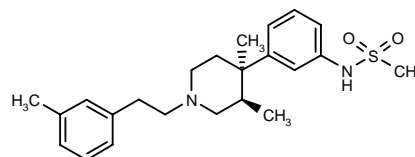
- Watson, B. et al. (Novo Nordisk A/S) *Novel 1,3,8-triazaspiro[4.5]decanones with high affinity for opioid receptor subtypes*. WO 9959997.

DERMATOLOGIC DRUGS

TREATMENT FOR ALLERGIC SKIN DISORDERS

283346

(±)-*cis*-N-[3-[3,4-Dimethyl-1-[2-(3-methylphenyl)ethyl]piperidin-4-yl]phenyl]methanesulfonamide



C₂₃ H₃₂ N₂ O₂ S; Mol wt: 400.5838

ACTION – Antipruritic agent found effective in a rat model of hindleg scratching induced by the known pruritogenic agent 5-methoxytryptamine hydrochloride. Potentially useful for the treatment of pruritic dermatoses including allergic dermatitis and atopy.

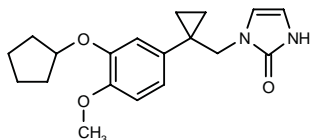
SOURCE – Pfizer.

REFERENCES

- Armer, R.E. et al. (Pfizer Inc.;Pfizer Ltd.) *Novel 4-phenylpiperidines for the treatment of pruritic dermatoses*. WO 9959971.

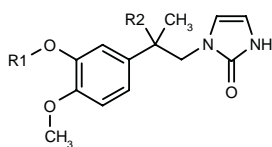
283553

1-[1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-cyclopropylmethyl]-2,3-dihydro-1H-imidazol-2-one



C19 H24 N2 O3; Mol wt: 328.4096

ACTION – Inhibitor of phosphodiesterase type 4 (PDE4) activity and cytokine, particularly TNF- α , production, potentially useful in the treatment of allergic, atopic and inflammatory disorders, particularly atopic dermatitis. Other specifically claimed 1,3-dihydro-1-(phenylalkyl)-2H-imidazol-2-one compounds are:



Compound	R1	R2	Formula
283554	cyclopentyl	Me	C ₁₉ H ₂₆ N ₂ O ₃
283556	cyclopentyl	H	C ₁₈ H ₂₄ N ₂ O ₃
283562	cyclopropyl-CH2	H	C ₁₇ H ₂₂ N ₂ O ₃

SOURCE – Janssen.

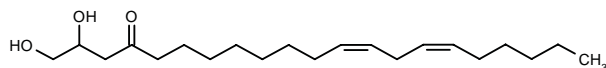
REFERENCES

1. Freyne, E.J.E. et al. (Janssen Pharmaceutica NV) 1,3-Dihydro-1-(phenylalkyl)-2H-imidazol-2-one cpds. and their use for treating allergic, atopic or inflammatory diseases. US 5994376, WO 9631485.

ANTIPSORIATICS

282477

1,2-Dihydroxyhenicosa-12(Z),15(Z)-dien-4-one



C21 H38 O3; Mol wt: 338.5282

ACTION – Compound extracted from vegetable oil, particularly avocado oil, with cell growth-inhibitory activity. It inhibited the proliferation of human skin fibroblasts by at least 50% at a concentration of 10 μ g/ml, while having no clear effect on collagen biosynthesis. Potentially useful for inhibiting nontumor cell proliferation, such as in ichthyoses, psoriasis and seborrheic keratoses, and in the treatment of rheumatoid arthritis, systemic lupus erythematosus, osteoporosis, arthrosis, gingivitis, liver fibrosis, cirrhosis and atherosclerosis.

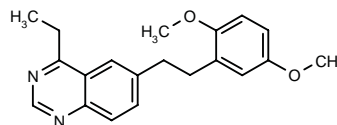
SOURCE – Pharmascience (France).

REFERENCES

1. Meriaux, E. et al. (Laboratoires Pharmascience) Novel cpds. extracted from vegetable oil using in pharmaceuticals and cosmetics, in particular for inhibiting cell growth. FR 2778181, WO 9955657.

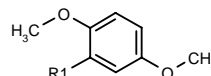
283171

6-[2-(2,5-Dimethoxyphenyl)ethyl]-4-ethylquinazoline



C20 H22 N2 O2; Mol wt: 322.4058

ACTION – Antiproliferative and antiinflammatory agent with nanomolar IC₅₀ values for inhibition of the proliferation of human keratinocyte HaCaT cells (IC₅₀ = 10 nM) and tumor cell lines such as human malignant melanoma A-375, human lung carcinoma A549, human breast adenocarcinoma MDA-MB-231, human colon adenocarcinoma SW-480, human breast carcinoma MDA-MB-435 and human colon adenocarcinoma HT-29 (IC₅₀ = 10-200 nM). Specifically claimed for the treatment of psoriasis. Other exemplified trisubstituted phenyl derivatives include the following:



Compound	R1	Formula
283172	3-(CO2Me)-4-(AcNH)-PhCH2CH2	C ₂₀ H ₂₃ NO ₅
283174	4-oxo-3,4-dihydro-6-quinazolinyl-NHCH2	C ₁₇ H ₁₇ N ₃ O ₃
283175	4-OH-3-(CO2Et)-6-quinoliny-CH2CH2	C ₂₂ H ₂₃ NO ₅
283176	3-[2,6-(MeO)2-PhCH2]-4-oxo-3,4-dihydro-6-quinazolinyl-OCH2	C ₂₆ H ₂₆ N ₂ O ₆
283177	4-MeO-6-quinazolinyl-CH=CH	C ₁₉ H ₁₈ N ₂ O ₃
283178	3-Me-4-oxo-3,4-dihydro-6-quinazolinyl-CH2CH2	C ₁₉ H ₂₀ N ₂ O ₃
283498	4-MeO-6-quinazolinyl-CH2CH2	C ₁₉ H ₂₀ N ₂ O ₃
283500	4-Me-6-quinazolinyl-CH2CH2	C ₁₉ H ₂₀ N ₂ O ₂

SOURCE – Novartis.

REFERENCES

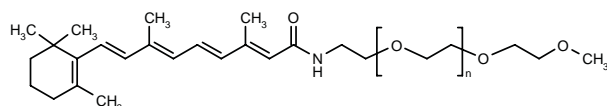
1. Nussbaumer, P. (Novartis AG) Trisubstd. phenyl derivs. US 5990116, WO 9628430.

OTHER DERMATOLOGIC DRUGS

281519

N-[2-[2-(2-Methoxyethoxy)poly(n=9-10)ethoxy]ethyl]-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2(*E*),4(*E*),6(*E*),8(*E*)-nonatetraenamide

Polyethoxylated (n = 9.8) retinamide



ACTION – Agent for inhibiting skin aging, a novel retinamide derivative that is nontoxic and nonirritating and exhibits enhanced skin absorption compared to retinol, retinol palmitate and retinoic acid, as well as the ability to increase collagen synthesis in human fibroblasts.

SOURCE – LG Chem.

REFERENCES

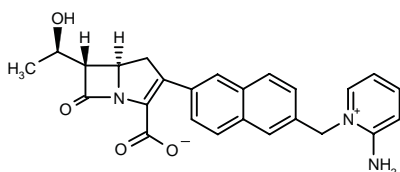
1. Chung, B.Y. et al. (LG Chem Ltd.) *Polyethoxylated retinamide derivs. and process for preparing the same*. WO 9950240.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

281643

(5*R*,6*S*)-2-[6-(2-Aminopyridinium-1-ylmethyl)naphth-2-yl]-6-[1(*R*)-hydroxyethyl]carbapen-2-em-3-carboxylate inner salt



C25 H23 N3 O4; Mol wt: 429.4737

ACTION – Carbapenem antibiotic with potent *in vitro* activity against Gram-positive and Gram-negative bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA; MIC₅₀ = 2 µg/ml) and methicillin-resistant coagulase-negative staphylococci (MRCNS; MIC₅₀ = 8 µg/ml); compound showed markedly improved potency relative to imipenem (MIC₅₀ = 32 and 128 µg/ml, respectively) and similar activity to vancomycin (MIC₅₀ = 2 and 4 µg/ml, respectively). The new 2-naphthylcarbapenem exhibited comparable activity to imipenem against Gram-negative bacteria, except *Pseudomonas aeruginosa*.

SOURCE – Merck & Co.

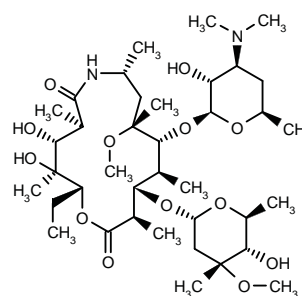
REFERENCES

1. DiNinno, F.P., Greenlee, M.L. (Merck & Co., Inc.) *2-Naphthyl-carbapenem antibacterial agents*. EP 466254, JP 92253980, US 5032587.

2. Greenlee, M.L. et al. *2-Naphthylcarbapenems: Broad spectrum antibiotics with enhanced potency against MRSA*. Bioorg Med Chem Lett 1999, 9(19): 2893.

281825

8a-Aza-8a-homo-6-*O*-methylerythromycin A



C38 H70 N2 O13; Mol wt: 762.9720

ACTION – A representative compound from a series of 15-membered lactam ketoazalides reported to display comparable or superior activity to erythromycin and clarithromycin against a wide range of microorganisms including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Moraxella catarrhalis*, *Campylobacter jejuni*, *Escherichia coli*, *Haemophilus influenzae* and *Listeria monocytogenes*.

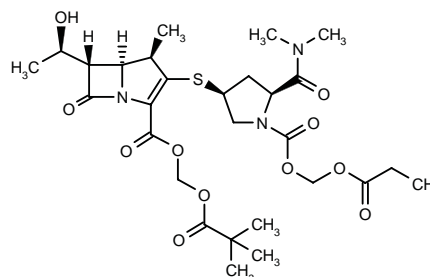
SOURCE – Pliva.

REFERENCES

1. Kobrehel, G. et al. (Pliva Pharmaceutical, Chem., Food & Cosmetic Ind., Inc.) *15-Membered lactams ketolides with antibacterial activity*. WO 9951616.

283496

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[5(*S*)-(N,N-dimethylcarbamoyl)-1-(propionyloxymethoxycarbonyl)pyrrolidin-3(*S*)-ylsulfanyl]carbapen-2-em-3-carboxylic acid pivaloyloxymethyl ester



C28 H41 N3 O11 S; Mol wt: 627.7079

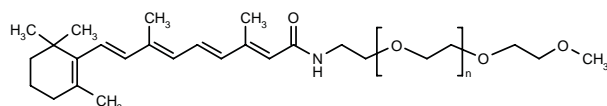
ACTION – Orally active, broad-spectrum carbapenem antibiotic. Another exemplified compound is:

OTHER DERMATOLOGIC DRUGS

281519

N-[2-[2-(2-Methoxyethoxy)poly(n=9-10)ethoxy]ethyl]-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2(*E*),4(*E*),6(*E*),8(*E*)-nonatetraenamide

Polyethoxylated (n = 9.8) retinamide



ACTION – Agent for inhibiting skin aging, a novel retinamide derivative that is nontoxic and nonirritating and exhibits enhanced skin absorption compared to retinol, retinol palmitate and retinoic acid, as well as the ability to increase collagen synthesis in human fibroblasts.

SOURCE – LG Chem.

REFERENCES

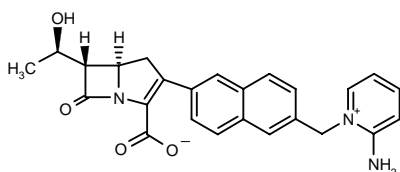
1. Chung, B.Y. et al. (LG Chem Ltd.) *Polyethoxylated retinamide derivs. and process for preparing the same*. WO 9950240.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

281643

(5*R*,6*S*)-2-[6-(2-Aminopyridinium-1-ylmethyl)naphth-2-yl]-6-[1(*R*)-hydroxyethyl]carbapen-2-em-3-carboxylate inner salt



C25 H23 N3 O4; Mol wt: 429.4737

ACTION – Carbapenem antibiotic with potent *in vitro* activity against Gram-positive and Gram-negative bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA; MIC₅₀ = 2 µg/ml) and methicillin-resistant coagulase-negative staphylococci (MRCNS; MIC₅₀ = 8 µg/ml); compound showed markedly improved potency relative to imipenem (MIC₅₀ = 32 and 128 µg/ml, respectively) and similar activity to vancomycin (MIC₅₀ = 2 and 4 µg/ml, respectively). The new 2-naphthylcarbapenem exhibited comparable activity to imipenem against Gram-negative bacteria, except *Pseudomonas aeruginosa*.

SOURCE – Merck & Co.

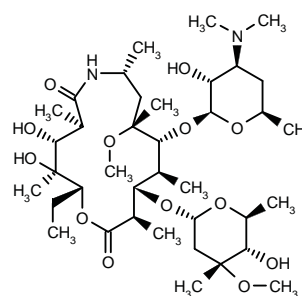
REFERENCES

1. DiNinno, F.P., Greenlee, M.L. (Merck & Co., Inc.) *2-Naphthyl-carbapenem antibacterial agents*. EP 466254, JP 92253980, US 5032587.

2. Greenlee, M.L. et al. *2-Naphthylcarbapenems: Broad spectrum antibiotics with enhanced potency against MRSA*. Bioorg Med Chem Lett 1999, 9(19): 2893.

281825

8a-Aza-8a-homo-6-*O*-methylerythromycin A



C38 H70 N2 O13; Mol wt: 762.9720

ACTION – A representative compound from a series of 15-membered lactam ketoazalides reported to display comparable or superior activity to erythromycin and clarithromycin against a wide range of microorganisms including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Moraxella catarrhalis*, *Campylobacter jejuni*, *Escherichia coli*, *Haemophilus influenzae* and *Listeria monocytogenes*.

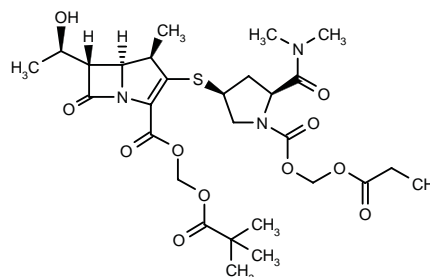
SOURCE – Pliva.

REFERENCES

1. Kobrehel, G. et al. (Pliva Pharmaceutical, Chem., Food & Cosmetic Ind., Inc.) *15-Membered lactams ketolides with antibacterial activity*. WO 9951616.

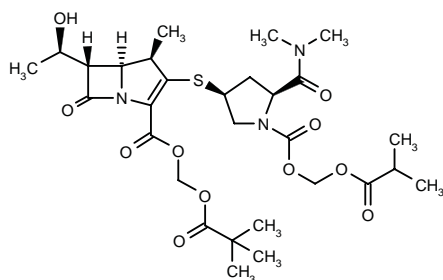
283496

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[5(*S*)-(N,N-dimethylcarbamoyl)-1-(propionyloxymethoxycarbonyl)pyrrolidin-3(*S*)-ylsulfanyl]carbapen-2-em-3-carboxylic acid pivaloyloxymethyl ester



C28 H41 N3 O11 S; Mol wt: 627.7079

ACTION – Orally active, broad-spectrum carbapenem antibiotic. Another exemplified compound is:



283497: C₂₉ H₄₃ N₃ O₁₁ S

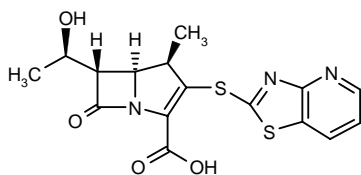
SOURCE – Kyoto Pharmaceutical.

REFERENCES

1. Matsui, H. (Kyoto Pharmaceutical Industries, Ltd.) *Carbapenem derivs., utilization thereof and intermediate cpds. of the same*. WO 9957121.

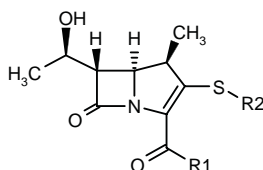
283631

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-(thiazolo[4,5-*b*]pyridin-2-ylsulfanyl)carbapen-2-em-3-carboxylic acid



C₁₆ H₁₅ N₃ O₄ S₂; Mol wt: 377.4435

ACTION – β -Lactam compound with excellent antibacterial activity against Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other representative compounds are:



Compound	R1	R2	Formula
283632	O-	5-(NH ₂ COCH ₂)-thiazolo[5,4- <i>c</i>]pyridinium-2-yl	C ₁₈ H ₁₈ N ₄ O ₅ S ₂
283633	OH	5-Me-4,5,6,7-tetrahydrothiazolo[5,4- <i>c</i>]pyridin-2-yl	C ₁₇ H ₂₁ N ₃ O ₄ S ₂
283635	OH	5,6,7,8-tetrahydro-4 <i>H</i> -thiazolo[4,5- <i>b</i>]azepin-2-yl	C ₁₇ H ₂₁ N ₃ O ₄ S ₂
283636	O-	5-(NH ₂ COCH ₂)-oxazolo[4,5- <i>c</i>]pyridinium-2-yl	C ₁₈ H ₁₈ N ₄ O ₆ S

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

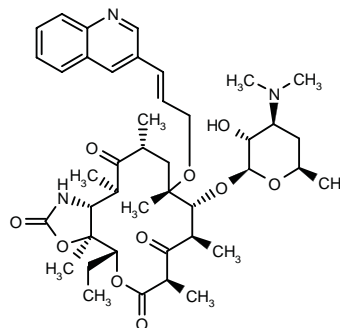
1. Sunagawa, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Novel β -lactam cpds. and process for producing the same*. WO 9958536.

ABT-773*

265173

(3*aS*,4*R*,7*R*,9*R*,10*R*,11*S*,13*R*,15*R*,15*aR*)-4-Ethyl-3*a*,7,9,11,13,15-hexamethyl-11-[3-(3-quinoliny)-2(*E*)-propenyloxy]-10-[3,4,6-trideoxy-3-(dimethylamino)- β -D-xylohexopyranosyloxy]octahydro-2*H*-oxacyclotetradecino-[4,3-*d*]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tetraone

A-195773.0



C₄₂ H₅₉ N₃ O₁₀; Mol wt: 765.9391

ACTION – Ketolide antibiotic with high activity against both macrolide-susceptible and -resistant respiratory tract pathogens including *Staphylococcus aureus* (with the exception of MLS constitutively resistant strains), *Streptococcus pyogenes*, *Streptococcus pneumoniae* (MIC₉₀ < 0.0005-0.004 μ g/ml and < 0.002-1 μ g/ml for susceptible and resistant streptococci, respectively), *Moraxella catarrhalis* and *Haemophilus influenzae*. Compound was also highly effective against *erm*-containing *S. pneumoniae* with inducible MLS_B resistance (MIC₉₀ = 0.015 μ g/ml), which are highly resistant to erythromycin, clindamycin, azithromycin and the ketolide TE-802 (MIC > 128 μ g/ml). It also displayed *in vitro* activity against *Helicobacter pylori* (MIC₉₀ = 0.25 μ g/ml), *Legionella pneumophila* isolates (MIC = 0.015 μ g/ml) and *Toxoplasma gondii* both *in vitro* and *in vivo* in murine models of acute toxoplasmosis. *In vivo* studies in acute systemic infections in mice and lung infections in rats demonstrated a therapeutic advantage for compound over azithromycin and the ketolide HMR-3647. Pharmacokinetic studies in mice, rats, monkeys and dogs following single i.v. or oral doses demonstrated good oral absorption, with an oral bioavailability ranging from 35.8% in monkeys to 60.0% in rats. Currently undergoing clinical evaluation.

SOURCES – Abbott; Taisho.

REFERENCES

1. Or, Y.S. et al. (Abbott Laboratories, Inc.) *6-O-Substd. ketolides having antibacterial activity*. EP 929563, US 5866549, WO 9809978.
2. Barry, A.L. et al. *Comparative in vitro antimicrobial activity of ABT-773 and tentative disk test interpretive criteria*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F2144.
3. Brueggemann, A.B. et al. *Comparative in vitro activity of a novel ketolide antimicrobial agent, ABT773 (ABT), and the activity of HMR4004 (HMR), erythromycin (ERY), clarithromycin (CLA) and azithromycin (AZI) versus Streptococcus pneumoniae*. Clin Microbiol Infect 1999, 5(Suppl. 3): Abst P176.
4. Bui, M.H. et al. *Antibacterial effects of ABT-773 against respiratory tract pathogens*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F2138.
5. Cao, Z. et al. *Mechanism of action for novel ketolide ABT773*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F2135.

6. Capobianco, J.O. et al. *Rapid drug accumulation of ABT-773 in Streptococcus pneumoniae*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F2137.

7. Ewing, P.A. et al. *Efficacy of ABT-773 against acute systemic bacterial infections in mice caused by resistant Streptococcus pneumoniae*. Clin Microbiol Infect 1999, 5(Suppl. 3): Abst P179.

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9. Guan, Z. et al. *In vitro and in vivo metabolism of [¹⁴C]ABT-773*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F2149.

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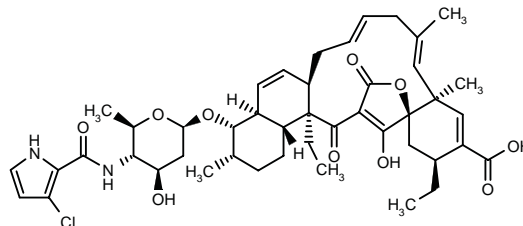
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*Identified compound **265173** (see **263812**) Drug Data Rep 1998, 020(07): 0600.

DECATROMICIN A

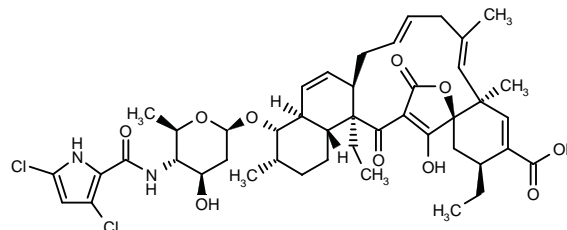
281043

4(S)-[5(S)-(3-Chloro-1H-pyrrol-2-ylcarboxamido)-4(R)-hydroxy-6(R)-methyltetrahydropyran-2(R)-yloxy]-15(S), 20a(R)-diethyl-21-hydroxy-3(S), 11, 12a(S)-trimethyl-18, 20-dioxo-2,3,4,4a(S), 6a(R), 7, 10, 12a, 15, 16, 18, 20, 20a, 20b(R)-tetradecahydro-1H-16a(R), 19-methenobenzo[b]-naphtho[2,1-j]oxacyclotetradecin-14-carboxylic acid



C45 H57 Cl N2 O10; Mol wt: 821.4023

ACTION – Antibiotic extracted from the culture broth of *Actinomadura* sp. MK73-NF4, active against Gram-positive bacteria including multidrug-resistant strains such as *Staphylococcus aureus* MS9610 and methicillin-resistant *S. aureus* (MIC = 3.13 and 1.56 μ g/ml, respectively). Compound did not inhibit the growth of Gram-negative bacteria or yeasts at 100 μ g/ml. Another compound isolated from this source and even more potent than title compound is:



Decatromicin B [281135]: C45 H56 Cl2 N2 O10

SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

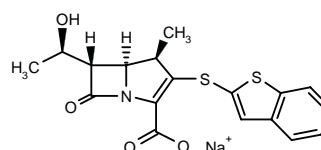
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J-110441

280728

(1R,5S,6S)-2-(1-Benzothien-2-ylsulfanyl)-6-[1(R)-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid sodium salt



C18 H16 N Na O4 S2; Mol wt: 397.4494

ACTION – Potent, broad-spectrum carbapenem β -lactamase inhibitor active against the metallo- β -lactamases IMP-1 (*Pseudomonas aeruginosa*), CcrA (*Bacteroides fragilis*), L1 (*Stenotrophomonas maltophilia*) and Type II (*Bacillus cereus*), with respective K_i values of 0.0037, 0.23, 1.00 and 0.83 μ M, as well as against class A (*Escherichia coli*) and class C (*Enterobacter cloacae*) serine β -lactamases, with K_i values of 2.54 and 0.037 μ M, respectively. Compound showed synergistic antibacterial activity with ceftazidime or imipenem against β -lactamase-producing strains. For example, it reduced the MIC of imipenem against IMP-1-producing isolates of *Serratia marcescens* and *P. aeruginosa* from 64–256 μ g/ml to 4–64 μ g/ml in the presence of 1/4 its MIC; it also reduced the MIC of ceftazidime against class C β -lactamase-producing *E. cloacae* from 64 μ g/ml to 4 μ g/ml in the presence of 1/8 its MIC.

SOURCE – Banyu.

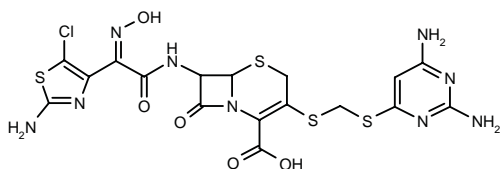
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3. Waddell, S.T. et al. Benzothiazolylthio carbapenems: Potent anti-MRSA agents. Bioorg Med Chem Lett 1995, 5(13): 1427.
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LB-10827

280723

7-[2-(2-Amino-5-chlorothiazol-4-yl)-2-(hydroxyimino)-acetamido]-3-(2,6-diaminopyrimidin-4-ylsulfanylmethyl-sulfanyl)-3-cephem-4-carboxylic acid



C17 H16 Cl N9 O5 S4; Mol wt: 590.0884

ACTION – Cephalosporin antibiotic with broad-spectrum activity against Gram-positive and Gram-negative bacteria including clinically resistant strains of respiratory pathogens such as penicillin-resistant *Streptococcus pneumoniae* (MIC₉₀ = 0.5 μ g/ml), quinolone-resistant *S. pneumoniae* (MIC₉₀ = 0.25 μ g/ml), β -lactamase-positive and -negative *Haemophilus influenzae* (MIC₉₀ = 0.25 and 0.5 μ g/ml, respectively) and *Moraxella catarrhalis* (MIC₉₀ = 0.13 μ g/ml); in comparison to β -lactams, macrolides and quinolones, compound was the most potent among the compounds tested against penicillin- and quinolone-resistant isolates of *S. pneumoniae*. In vivo in neutropenic rats with pneumonia, at a dose of 2 mg/kg p.o., it showed better therapeutic efficacy than trovafloxacin and cefdinir at 50 mg/kg p.o. and amoxicillin/clavulanic acid 10 mg/kg p.o. in reducing viable bacterial counts in lungs. In a murine model of infection induced by intranasal instillation

of the bacteria, compound was as effective as amoxicillin/clavulanic acid and more effective than the other two antibiotics. Excellent pharmacokinetic properties were seen in rats, with good oral bioavailability (56%).

SOURCE – LG Chem.

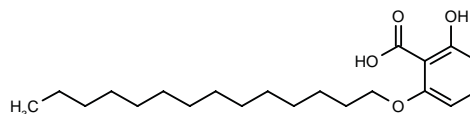
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ANTIBACTERIAL DRUGS

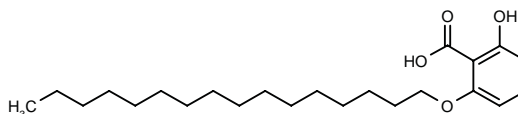
274044

2-Hydroxy-6-(tetradecyloxy)benzoic acid



C21 H34 O4; Mol wt: 350.4956

ACTION – Antibacterial agent, an inhibitor of bacterial histidine protein kinase (HPK)-mediated two-component regulatory systems (TCS) that is able to inhibit the autophosphorylation of KinA and/or the transphosphorylation of Spo0F, the sporulation-regulatory TCS protein from *Bacillus subtilis* (IC₅₀ = 2.2 μ M), as well as the autophosphorylation of NRII and/or the transphosphorylation of NRI, the nitrogen-regulatory TCS protein from *Escherichia coli* (IC₅₀ = 5 μ M). Compound showed good antibacterial activity against *Enterococcus faecalis* and vancomycin-resistant *Enterococcus faecium* (MIC = 4 μ g/ml). Within this series of 6-oxa isosteres of anacardic acid, the following is also included:



274046: C23 H38 O4

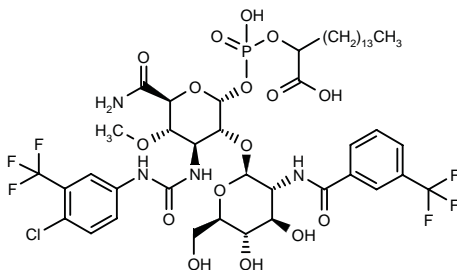
SOURCE – R.W. Johnson.

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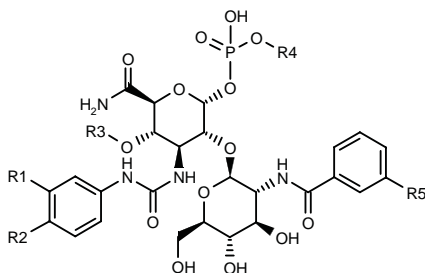
280003

2-[[3-[N'-[4-Chloro-3-(trifluoromethyl)phenyl]ureido]-3-deoxy-2-O-[2-deoxy-2-[3-(trifluoromethyl)benzamido]-β-D-glucopyranosyl]-4-O-methyl-α-D-glucopyranos-1-yloxyuronamide](hydroxy)phosphoryloxy]hexadecanoic acid



C45 H62 Cl F6 N4 O16 P; Mol wt: 1095.4120

ACTION – Disaccharide antibacterial agent with potent inhibitory activity against bacterial cell wall biosynthesis (IC_{50} = 9.2 µg/ml in a peptidoglycan polymerization assay) and potent antibacterial activity against a variety of antibiotic-sensitive and -resistant Gram-positive bacteria including *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus* (MIC = 3.12, 3.12 and 6.25 µg/ml, respectively), methicillin-resistant *S. aureus* (MIC = 3.12 µg/ml), vancomycin-resistant *E. faecium* (MIC = 3.12-6.25 µg/ml) and vancomycin-resistant *E. faecalis* (MIC = 3.12-6.25 µg/ml). Compound was shown to be equipotent to vancomycin as an inhibitor of cell wall biosynthesis and against the panel of antibiotic-sensitive Gram-positive bacteria, but it was more effective than reference antibiotic against clinically relevant antibiotic-resistant enterococci. Other representative compounds within this series of moenomycin disaccharide analogues are:



Compound	R1	R2	R3	R4	R5	Formula
280005	CF3	Cl	Me	(R)-CH2C(CO2H)-OC12H25	H	C ₄₃ H ₆₁ ClF ₃ N ₄ O ₁₇ P
280006	CF3	Cl	Me	C12H25	CF3	C ₄₁ H ₅₆ ClF ₃ N ₄ O ₁₄ P
280007	CF3	Cl	H	(R)-CH2C(CO2H)-OC12H25	CF3	C ₄₃ H ₅₈ ClF ₃ N ₄ O ₁₇ P
280008	CF3	Cl	H	C12H25	CF3	C ₄₀ H ₅₄ ClF ₃ N ₄ O ₁₄ P
280009	H	OCF3	H	(R)-CH2C(CO2H)-OC12H25	CF3	C ₄₃ H ₅₉ F ₆ N ₄ O ₁₈ P

SOURCE – Incara.

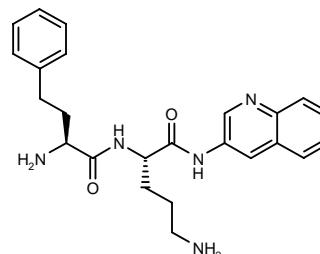
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281011^{2,3}

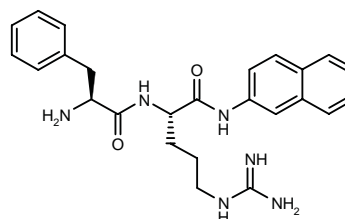
5-Amino-2(S)-[2(S)-amino-4-phenylbutyramido]-N-(3-quinolyl)pentanamide

L-Homophenylalanyl-N¹-(3-quinolyl)-L-ornithinamide



C24 H29 N5 O2; Mol wt: 419.5261

ACTION – Broad-spectrum efflux pump inhibitor with minimal intrinsic activity against *Pseudomonas aeruginosa* PAM 1032 overexpressing the MexAB-OprM efflux pump, but which is able to potentiate the activity of levofloxacin against *P. aeruginosa* strains PAM 1032, PAM 1033 (overexpressing the MexCD-OprJ efflux pump) and *P. aeruginosa* PAM 1034 (overexpressing the MexEF-OprN efflux pump) by 8-fold at concentrations of 2.5-5 µg/ml. Another related compound is:



MC-207,110 [281012]¹⁻³: C25 H30 N6 O2

SOURCES – Daiichi Pharmaceutical; Microcide.

REFERENCES

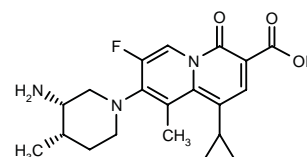
1. Chamberland, S. et al. (Microcide Pharmaceuticals, Inc.) *Efflux pump inhibitors*. EP 823942, WO 9633285.

2. Renau, T.E. et al. *Inhibitors of efflux pumps in Pseudomonas aeruginosa potentiate the activity of the fluoroquinolone antibacterial levofloxacin*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abstr F1265.

3. Renau, T.E. et al. *Inhibitors of efflux pumps in Pseudomonas aeruginosa potentiate the activity of the fluoroquinolone antibacterial levofloxacin*. J Med Chem 1999, 42(24): 4928.

281390

cis-8-(3-Amino-4-methylpiperidiny)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4H-quinolizine-3-carboxylic acid



C20 H24 F N3 O3; Mol wt: 373.4256

ACTION – Oxoquinolizone antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative strains including *Staphylococcus aureus* NCTC 10649M (MIC = 0.05 µg/ml), *Enterococcus faecium* ATCC 8043 (MIC = 0.2 µg/ml), *Pseudomonas aeruginosa* 5007 (MIC = 0.78 µg/ml) and drug-resistant strains such as *S. aureus* 1775 (MIC = 1.56 µg/ml), *Streptococcus pyogenes* 930 (MIC = 0.1 µg/ml), *Escherichia coli* KNK 437 (MIC = 0.39 µg/ml), *P. aeruginosa* DPHP 5263 (MIC = 12.5 µg/ml) and *Pseudomonas cepacia* 2961 (MIC = 1.56 µg/ml). Good *in vivo* efficacy was observed against murine infections caused by *S. aureus* NCTC 10649M (ED₅₀ = 3.3 and 0.8 mg/kg s.c. and p.o., respectively), *Streptococcus pneumoniae* ATCC 6303 (ED₅₀ = 1.0 and 2.0 mg/kg s.c. and p.o., respectively) and *E. coli* JUHL (ED₅₀ = 0.6 and 1.4 mg/kg s.c. and p.o., respectively).

SOURCE – Abbott.

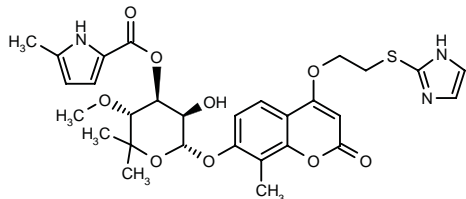
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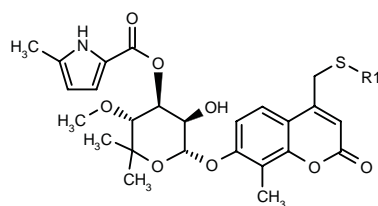
281632

7-[6-Deoxy-4-O,5-dimethyl-3-O-(5-methyl-1H-pyrrol-2-ylcarbonyl)-α-L-mannopyranosyloxy]-4-[2-(1H-imidazol-2-ylsulfanyl)ethoxy]-8-methyl-2H-1-benzopyran-2-one



C29 H33 N3 O9 S; Mol wt: 599.6577

ACTION – Antibacterial agent, a DNA gyrase inhibitor that is at least 3-fold more potent than novobiocin in inhibiting the supercoiling activity of *Escherichia coli* DNA gyrase. Compound was active against Gram-positive bacteria including *Staphylococcus aureus* 011HT3 and *Streptococcus pyogenes* 02A1UC1 (MIC = 0.08 and 0.6 µg/ml, respectively), oxacillin/teicoplanin-resistant *Staphylococcus epidermidis* 012GO39 (MIC = 0.04 µg/ml or less) and novobiocin-resistant *S. aureus* 011HT1 (MIC = 2.5 µg/ml), as well as against multidrug-resistant *S. aureus* 011GO76 (MIC = 5 µg/ml) and *Enterococcus faecium* 02D31P2 (MIC = 5 µg/ml). Other representative compounds within this series of aminoalkyl substituted coumarins are:



Compound	R1	Formula
281630	2-imidazolyl	C ₂₈ H ₃₁ N ₃ O ₈ S
281631	1,2,4-triazol-3-yl	C ₂₇ H ₃₀ N ₄ O ₈ S

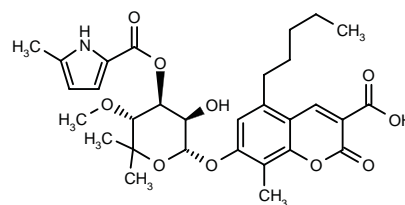
SOURCE – Aventis Pharma.

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281633

7-[6-Deoxy-4-O,5-dimethyl-3-O-(5-methyl-1H-pyrrol-2-ylcarbonyl)-α-L-mannopyranosyloxy]-8-methyl-2-oxo-5-pentyl-2H-1-benzopyran-3-carboxylic acid



C30 H37 N O10; Mol wt: 571.6193

ACTION – Antibacterial agent, an inhibitor of DNA gyrase with similar inhibition of negative supercoiling of DNA gyrase to novobiocin but superior antibacterial activity. Compound exhibited excellent antibacterial activity against *Staphylococcus aureus* 011HT3 (MIC = 0.04 µg/ml or less) and *Streptococcus pyogenes* 02A1UC1 (MIC = 0.04 µg/ml or less), and the multidrug-resistant strains *S. aureus* 011GO76 (MIC = 0.15 µg/ml), *Staphylococcus epidermidis* 012GO39 (MIC = 0.04 µg/ml or less), *S. aureus* 011HT1 (MIC = 2.5 µg/ml) and *Enterococcus faecium* 02D31P2 (MIC = 0.3 µg/ml).

SOURCE – Aventis Pharma.

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283274**L-Prolyl-L-tryptophyl-L-lysyl-L-tryptophyl-L-prolyl-L-tryptophyl-L-tryptophyl-L-prolyl-L-tryptophyl-L-arginyl-L-argininamide**

C88 H110 N24 O11; Mol wt: 1679.9940

ACTION – Antimicrobial agent, an analogue of the naturally occurring peptide indolicidin that exhibits activity against protozoa such as *Giardia lamblia*, *Chlamydia* spp. and *Acanthamoeba* spp., viruses, particularly HIV-1, yeast and fungi such as *Cryptococcus* and *Candida* spp., various Gram-negative and Gram-positive bacteria including *Escherichia*, *Salmonella* and *Staphylococcus* spp., and helminths such as liver flukes.

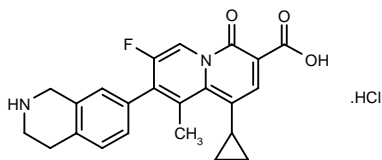
SOURCE – University of California, Oakland, Oakland, CA (US).

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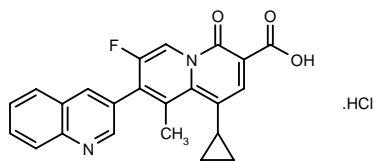
A-255916**280730**

1-Cyclopropyl-7-fluoro-9-methyl-4-oxo-8-(1,2,3,4-tetrahydro-7-isoquinolinyl)-4H-quinolizine-3-carboxylic acid hydrochloride



C23 H21 F N2 O3 . HCl; Mol wt: 428.8888

ACTION – Antibacterial agent with potent *in vitro* activity against Gram-positive strains including *Staphylococcus aureus* ATCC 6538P and *S. aureus* 1775 (MIC = 0.02 and 0.78 µg/ml, respectively), *Enterococcus faecium* (MIC = 0.05 µg/ml) and *Streptococcus pyogenes* (MIC = 0.05 µg/ml) and superior antibacterial activity compared to ciprofloxacin (MIC = 0.39, > 100, 0.78 and 1.56 µg/ml, respectively). Compound also exhibited good activity against Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa* (MIC = 0.05 and 0.78 µg/ml, respectively). In comparison with the parent compound ABT-719, it showed an improved safety profile while maintaining potent antibacterial activity. Another 8-C-linked 2-pyridone with a similar profile of activity is:

**A-238086.0 [280731]:** C23 H17 F N2 O3 . HCl**SOURCE** – Abbott.**REFERENCES**

1. Schultz, C.C. et al. *Synthesis and antibacterial activity of C-8 carbon-linked 2-pyridones*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F560.

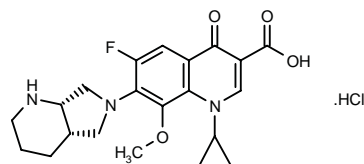
MOXIFLOXACIN HYDROCHLORIDE

Prop INNM

240775

(1'S,6'S)-1-Cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride

(4a*S*,7a*S*)-1-Cyclopropyl-6-fluoro-8-methoxy-7-(octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride

Bay-12-8039⁺

C21 H24 F N3 O4 . HCl; Mol wt: 437.9030

ACTION – Fluoroquinolone antibacterial agent.

INDICATION – Treatment of major respiratory infections including acute exacerbations of chronic bronchitis, acute sinusitis and community-acquired pneumonia.

PRESENTATION – Tablets, 436.8 mg equivalent to 400 mg moxifloxacin.

PROPRIETARY NAME – Avalox (DE).**SOURCE** – Bayer.**RECENT REFERENCES**

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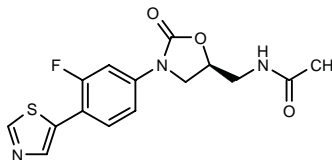
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*Drug Data Rep 1996, 018(10): 0915.

PNU-176968

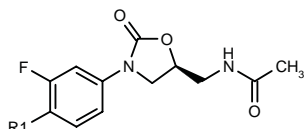
280994

N-[3-[3-Fluoro-4-(5-thiazolyl)phenyl]-2-oxooxazolidin-5(S)-ylmethyl]acetamide



C15 H14 F N3 O3 S; Mol wt: 335.3576

ACTION – Oxazolidinone antibacterial agent with potent activity against Gram-positive and fastidious Gram-negative bacteria including methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MIC = 0.5 µg/ml), *Staphylococcus epidermidis* and *Streptococcus pneumoniae* (MIC = 0.125 µg/ml or less), *Enterococcus faecalis*, *Haemophilus influenzae* and *Moraxella catarrhalis* (MIC = 0.5, 4 and 1 µg/ml, respectively). Compound showed good efficacy against lethal systemic *S. aureus* infections in mice (ED₅₀ = 4.3 mg/kg p.o.). Within this series of carbon-carbon-linked heteroarylphenyl oxazolidinone analogues, the following are also included:



Compound	R1	Formula
280995	5-CH ₂ -2-thienyl	C ₁₇ H ₁₄ FN ₃ O ₃ S
280996	3-Me-5-isoxazolyl	C ₁₆ H ₁₆ FN ₃ O ₄

SOURCE – Pharmacia & Upjohn (Pharmacia).

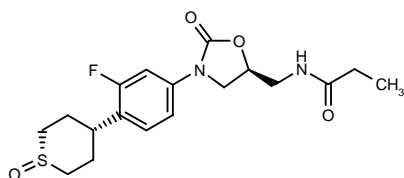
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PNU-179954^{*,1-4}

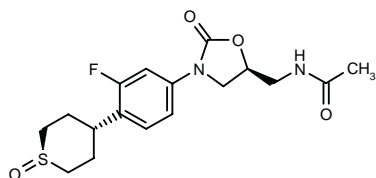
277823

(-)-*trans*-N-[3-[3-Fluoro-4-(1-oxidoperhydrothiopyran-4-yl)phenyl]-2-oxooxazolidin-5(S)-ylmethyl]propionamide



C₁₈ H₂₃ F N₂ O₄ S; Mol wt: 382.4537

ACTION – Phenyloxazolidinone antibacterial agent with broad-spectrum activity against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* UC No. 9213 (MIC = 4 µg/ml), *Haemophilus influenzae* UC No. 30063 (MIC = 4 µg/ml) and *Moraxella catarrhalis* 30610 (MIC = 16 µg/ml), as well as methicillin-resistant *S. aureus* UC No. 12673 (MIC = 2-4 µg/ml) and methicillin-resistant *Staphylococcus epidermidis* UC No. 12084 (MIC = 0.5-2 µg/ml). Compound exhibited a good pharmacokinetic profile, with high absolute oral bioavailability (55%) following an oral dose of 20 mg/kg and good *in vivo* efficacy against systemic *S. aureus* infections in mice (ED₅₀ = 2.5 mg/kg p.o.). Another phenyloxazolidinone is:



PNU-176723 [277819]^{**,1,2,4}: C₁₇ H₂₁ F N₂ O₄ S

SOURCE – Pharmacia & Upjohn (Pharmacia).

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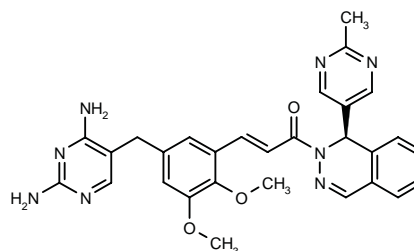
*Identified compound 277823 (see 277818) Drug Data Rep 1999, 021(08): 0713.

**Identified compound 277819 (see 277818) Drug Data Rep 1999, 021(08): 0713.

RO-64-5781²⁻⁴

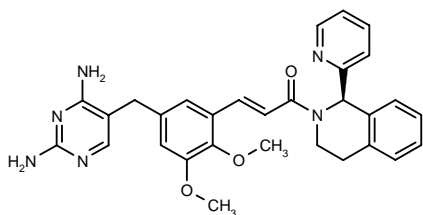
280856

3-[5-(2,4-Diaminopyrimidin-5-ylmethyl)-2,3-dimethoxyphenyl]-1-[1(R)-(2-methylpyrimidin-5-yl)-1,2-dihydrophthalazin-2-yl]-2(E)-propen-1-one



C₂₉ H₂₈ N₈ O₃; Mol wt: 536.5932

ACTION – Antibacterial agent, an inhibitor of dihydrofolate reductase (DHFR) active against both trimethoprim-sensitive and trimethoprim-resistant DHFR from *Staphylococcus aureus* (IC₅₀ = 0.1 nM) and trimethoprim-resistant DHFR from *Streptococcus pneumoniae* (IC₅₀ = 0.4 nM) and showing excellent selectivity for the bacterial enzyme with respect to the human enzyme. Compound showed good *in vitro* activity against staphylococci including multidrug-resistant strains (MIC₉₀ = 0.03-0.5 µg/ml), pneumococci, Gram-negative species including *Legionella pneumophila* (MIC = 0.015 µg/ml or less), *Moraxella catarrhalis* (MIC = 0.25 µg/ml) and *Haemophilus influenzae* (MIC = 1 µg/ml), as well as *Mycobacterium species*, especially *Mycobacterium avium intracellulare* (MIC = 0.125 µg/ml). It was very effective in murine models of septicemia caused by both trimethoprim-sensitive and -resistant strains of *S. aureus* (ED₅₀ = 0.36 and 4 mg/kg i.v., respectively). Another representative compound within this series of 2,4-diamino-pyrimidine derivatives is:



Ro-62-6091 [280855]^{1,3,4}: C30 H30 N6 O3

SOURCE – Roche.

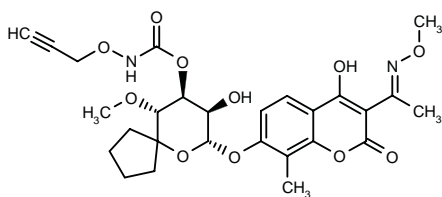
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RU-79115*,1-3

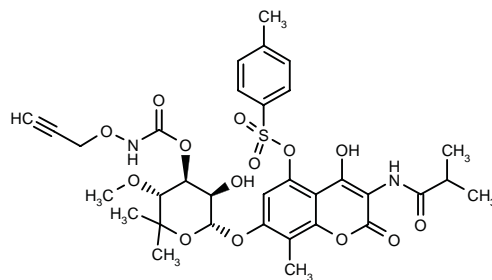
278873

2-Propynyloxycarbamic acid 7(*R*)-[4-hydroxy-3-(*N*-methoxyacetimidoyl)-8-methyl-2-oxo-2*H*-1-benzopyran-7-yloxy]-8(*R*)-hydroxy-10(*R*)-methoxy-6-oxaspiro[4.5]dec-9(*S*)-yl ester



C27 H32 N2 O11; Mol wt: 560.5528

ACTION – Coumarin antibiotic, an inhibitor of bacterial DNA gyrase B (IC_{50} = 0.015 μ g/ml against *Staphylococcus aureus* enzyme) with *in vitro* antibacterial activity against staphylococci including β -lactam- and quinolone-resistant strains (MIC_{50} = 0.08 μ g/ml), streptococci (MIC_{50} = 0.6 μ g/ml) including penicillin-resistant pneumococci (MIC_{50} = 0.15 μ g/ml) and vancomycin-resistant enterococci (MIC_{50} = 0.3 μ g/ml). In comparison to vancomycin, compound showed up to 8-fold greater activity against staphylococci and similar activity against streptococci including penicillin-resistant pneumococci. Compound was seen to protect from murine septicemia caused by Gram-positive bacteria, including vancomycin-resistant enterococci, giving PD_{50} values of 1-40 mg/kg s.c. In contrast with previous coumarinic antibiotics, no antivitamin K activity was observed up to 100 mg/kg p.o. and no signs of toxicity were observed in the CNS, cardiovascular and respiratory systems. Another related compound is:



RU-78535 [280738]²: C33 H38 N2 O14 S

SOURCE – Aventis Pharma.

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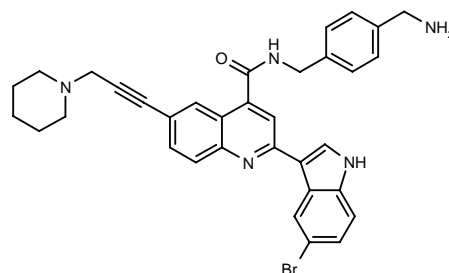
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*Identified compound **278873** (see **278868**) Drug Data Rep 1999, 021(10): 0906.

SEP-32196*,1-3

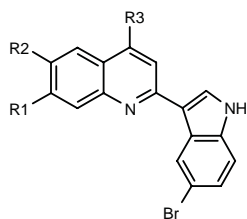
274409

N-[4-(Aminomethyl)benzyl]-2-(5-bromo-1*H*-indol-3-yl)-6-[3-(1-piperidinyl)-1-propynyl]quinoline-4-carboxamide



C34 H32 Br N5 O; Mol wt: 606.5648

ACTION – Antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* including methicillin-resistant isolates and isolates with intermediate vancomycin susceptibility (MIC_{90} = 1.56-6.25 μ g/ml), *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (MIC = 1.56, 3.1, 6.3 and 1.56 μ g/ml, respectively). It showed good tissue distribution and bioavailability after i.p. administration in mice and protected against intra-peritoneal infections caused by *S. aureus* (80 and 90% survival rate at 20 and 40 mg/kg i.p., respectively). Within this series of quinoline-indoles, the following are also included:



Compound	R1	R2	R3	Formula
SEP-132617 [274417] ^{**1,4}	Cl	1-Pip-CH2-ethynylene	CONHCH2-CH2NH2	C ₂₈ H ₂₇ BrClN ₅ O
SEP-137199 [280858] ¹⁻³	F	H	CH2OH	C ₁₈ H ₁₂ BrFN ₂ O

SOURCE – Sepracor.

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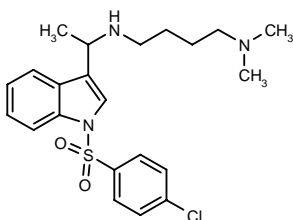
^{*}Identified compound **274409** (see **274405**) Drug Data Rep 1999, 021(04): 0340.

^{**}Identified compound **274417** (see **274405**) Drug Data Rep 1999, 021(04): 0340.

UK-57562-01

280791

*N*¹-[1-[1-(4-Chlorophenylsulfonyl)-1*H*-indol-3-yl]ethyl]-*N*⁴,*N*⁴-dimethylbutane-1,4-diamine



C₂₂ H₂₈ Cl N₃ O₂ S; Mol wt: 434.0012

ACTION – Tetracycline efflux-reversing agent able to reduce, at sub-MIC concentrations, the MICs of tetracycline by up to 8-fold against *Escherichia coli* strains carrying Tet A, Tet B, Tet C, Tet D, Tet K and Tet L resistance determinants. Compound was also able to reduce tetracycline MICs by up to 32-fold against resistant isolates of *Pasteurella haemolytica* and *Pasteurella multocida*. It lacks antibacterial activity when given alone (MIC = 50 µg/ml or more).

SOURCE – Pfizer.

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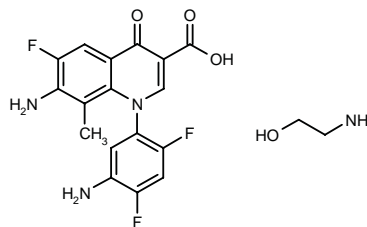
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WQ-3345*

267082

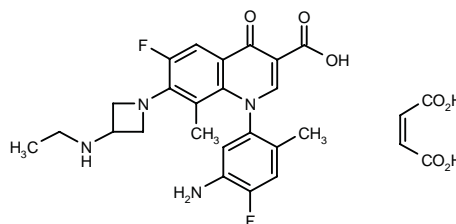
7-Amino-1-(5-amino-2,4-difluorophenyl)-6-fluoro-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethanolamine salt

WQ-2942 (as free acid)



C₁₇ H₁₂ F₃ N₃ O₃ . C₂ H₇ N O; Mol wt: 424.3771

ACTION – Quinolone antibacterial agent with broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria including quinolone-resistant strains and superior activity to the reference compounds ciprofloxacin, levofloxacin, sparfloxacin and trovafloxacin. Compound showed high efficacy, similar or superior to levofloxacin and sparfloxacin, against systemic and pulmonary infections in mice, in particular against infections caused by *Pseudomonas aeruginosa* (ED₅₀ = 4.23 mg/kg p.o.). It displayed good oral absorption in both mice and dogs and no phototoxicity was seen in mice. Selected as a candidate for clinical development. Another related 8-methylquinolone is:



WQ-3331 [280744]: C₂₃ H₂₄ F₂ N₄ O₃ . C₄ H₄ O₄

WQ-3330 (as free base)

SOURCE – Wakunaga.

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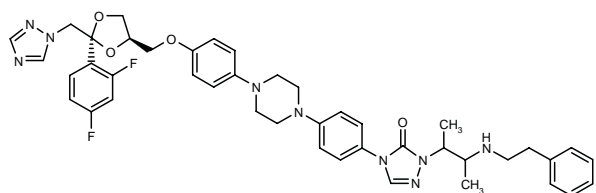
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^{*}Identified compound **267082** (see **266178**) Drug Data Rep 1998, 020(09): 0791.

ANTIFUNGAL AGENTS

283280

4-[4-[4-[4-[2(S)-(2,4-Difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4(R)-ylmethoxy]phenyl]piperazin-1-yl]phenyl]-2-[1-methyl-2-(2-phenylethylamino)propyl]-3,4-dihydro-2H-1,2,4-triazol-3-one



C43 H47 F2 N9 O4; Mol wt: 791.8993

ACTION – Water-soluble azole antifungal agent with a broad spectrum of activity, reported to be active against *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans*, *Sporothrix schenckii*, *Epidermophyton floccosum*, *Microsporum canis*, *Trichophyton* spp. and *Fusarium* spp. (MIC = 0.01-10 µM), its improved activity against the latter being of particular interest. Compound is chemically stable, has good oral availability and is not only fungistatic, like most azoles, but also fungicidal.

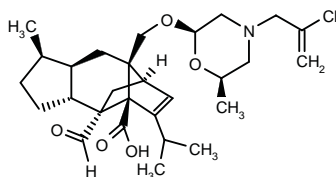
SOURCE – Janssen.

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283343

[1R-(1α,3αβ,4β,4αβ,7β,7αα,8αβ)]-8a-[4-(2-Chloroallyl)-6(R)-methylmorpholin-2(R)-yloxymethyl]-4-formyl-3-isopropyl-7-methyl-1,3a,4,4a,5,6,7,7a,8,8a-decahydro-1,4-methanoindacene-3a-carboxylic acid



C28 H40 Cl N O5; Mol wt: 506.0790

ACTION – Antifungal sordarin derivative particularly useful against *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Pneumocystis carinii*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Histoplasma capsulatum* and *Blastomyces dermatitidis*. It gave MIC values of < 0.001-0.03 µg/ml against most *Candida* spp. tested.

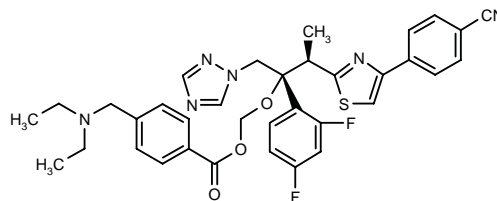
SOURCE – Glaxo Wellcome.

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283661

4-(Diethylaminomethyl)benzoic acid 2(R)-[4-(4-cyano-phenyl)thiazol-2-yl]-1(R)-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-ylmethyl)propoxymethyl ester



C35 H34 F2 N6 O3 S; Mol wt: 656.7546

ACTION – Water-soluble prodrug of the triazole antifungal BMS-207147 (ER-30346⁺) useful for the treatment of topical fungal infections including those caused by species of *Candida*, *Trichophyton*, *Microsporum* or *Epidermophyton*, as well as for mucosal infections caused by *Candida albicans* and systemic fungal infections caused by species of *C. albicans*, *Cryptococcus neoformans*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Coccidioides*, *Paracoccidioides*, *Histoplasma* or *Blastomyces*. It was shown to substantially increase the solubility (from < 0.006 mg/ml to > 1 mg/ml) and the release of BMS-207147 in rat and human plasma.

SOURCE – Bristol-Myers Squibb.

REFERENCES

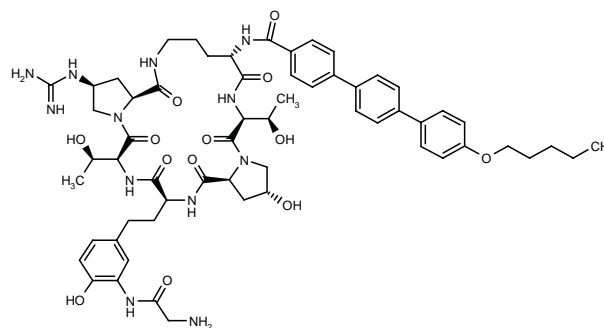
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*Drug Data Rep 1995, 017(11): 1031.

A-192411.29

280987

(2R,6S,9S,14aS,16S,20S,23S,25aS)-23-[2-[3-(2-Aminoacetamido)-4-hydroxyphenyl]ethyl]-6,20-bis[1(R)-hydroxyethyl]-16-guanidino-2-hydroxy-9-[4-[4'-pentyloxybiphenyl-4-yl]benzamido]perhydrodipyrrolo-[2,1-c:2,1-f][1,4,7,10,13,16]hexaazacycloheptacosine-5,8,14,19,22,25-hexone



C60 H78 N12 O13; Mol wt: 1175.3470

ACTION – Antifungal agent derived from the natural product echinocandin, with broad-spectrum fungicidal activity against a number of yeasts including *Candida albicans*, *Candida tropicalis* and *Candida glabrata* and potency comparable to that of amphotericin B; it was also active against *Cryptococcus neoformans* and against fluconazole- and amphotericin B-resistant *Candida* strains. Good *in vivo* activity in mice with systemic candidiasis has also been reported.

SOURCE – Abbott.

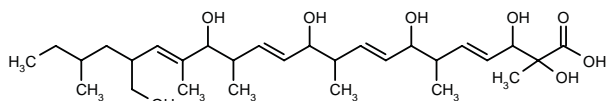
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BE-54753

283433

2,3,7,11,15-Pentahydroxy-18-(hydroxymethyl)-2,6,10,14,16,20-hexamethyldocosa-4(*E*),8(*E*),12(*E*),16(*E*)-tetraenoic acid



C29 H50 O8; Mol wt: 526.7060

ACTION – Antifungal substance isolated from *Chaetomium venezuelense* F54753 (FERM P-15626), proven active against *Saccharomyces cerevisiae*, *Candida albicans*, *Aspergillus niger* and other fungi (MIC = 12.5-25.0 µg/ml).

SOURCE – Banyu.

REFERENCES

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MC-510,027

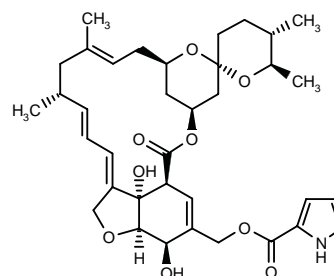
280999

(2'*S*,5'*S*,6*S*,6'*R*,7*S*,11*R*,13*S*,15*S*,17*aR*,20*R*,20*aR*,20*bS*)-20,20*b*-Dihydroxy-19-(pyrrol-2-ylcarboxymethyl)-5',6,6',8-tetramethyl-3',4',5',6',6,7,10,11,14,15,17,17*a*,20*a*,20*b*-tetradecahydrospiro[11,15-methano-2*H*,13*H*,20*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecino-13,2'-2*H*-pyran]-17-one

(6*R*,25*R*)-5-*O*-Demethyl-28-deoxy-6,28-epoxy-25-methyl-27-(pyrrol-2-ylcarboxy)milbemycin B

Antibiotic B 41C1

Milbemycin α-9



C36 H47 N O9; Mol wt: 637.7653

ACTION – An inhibitor of CDR-type fungal efflux pumps (ABC transporters) able to enhance the activity of azoles and terbinafine against wild-type *Candida albicans* and *C. albicans* overexpressing ABC transporters (MIC₉₀ > 128 and > 32 µg/ml, respectively, for fluconazole and terbinafine alone and 8 and 4 µg/ml, respectively, for fluconazole and terbinafine plus 10 µg/ml compound); it was also able to enhance the activity of azoles and terbinafine against wild-type *Candida glabrata* and *C. glabrata* overexpressing ABC transporters (CgCDR1 and CgCDR2), as well as against recent clinical isolates of *Candida* including *C. albicans*, *C. glabrata*, *Candida krusei* and *Candida tropicalis*.

SOURCE – Microcide.

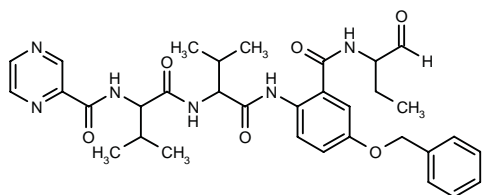
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ANTIVIRAL DRUGS

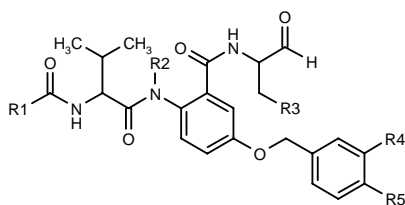
281505

5-Benzyloxy-*N*-(1-formylpropyl)-2-(pyrazin-2-ylcarbonyl-DL-valyl-DL-valylamino)benzamide



C33 H40 N6 O6; Mol wt: 616.7150

ACTION – Antiviral agent particularly suitable for the treatment of hepatitis C virus (HCV) infections, an inhibitor of serine proteases, particularly HCV NS3 protease (K_i in the range 1-100 μ M). Other exemplified compounds include the following:



Compound	R1	R2	R3	R4=R5	Formula
281506	2-pyrazinyl- -CONHCH(i-Pr)	H	CF3	H	C ₃₃ H ₃₇ F ₃ N ₆ O ₆
281507	2-pyrazinyl- -CONHCH(i-Pr)	Me	Me	H	C ₃₄ H ₄₂ N ₆ O ₆
281508	2-OH-1-Naph	H	Me	H	C ₃₄ H ₃₅ N ₃ O ₆
281509	6-OH-3-Pyr	H	Me	H	C ₂₉ H ₃₂ N ₄ O ₆
281510	6-OH-1-Naph	H	Me	H	C ₃₄ H ₃₅ N ₃ O ₆
281511	2-pyrazinyl- -CONHCH(i-Pr)	H	Me	Cl	C ₃₃ H ₃₈ Cl ₂ N ₆ O ₆

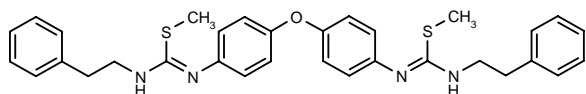
SOURCE – Vertex.

REFERENCES

1. Tung, R.D. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease*. WO 9950230.

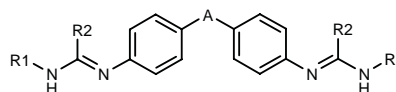
281669

3,3'-Oxybis(1,4-phenylene)bis[2-methyl-1-(2-phenylethyl)isothiourrea]

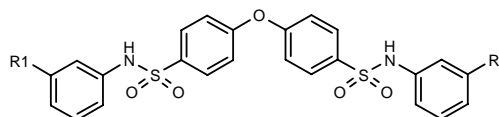


C32 H34 N4 O S2; Mol wt: 554.7796

ACTION – Antiviral agent found to significantly inhibit the replication of herpes simplex virus type 1 (HSV-1; > 90% inhibition at 30 μ M) and type 2 (HSV-2; > 50% at 10 μ M), and varicella-zoster virus (> 90% at 2 μ M). Other specifically claimed polyaromatic compounds are:



Compound	R1	R2	A	Formula
281670	Ph	SMe	O	C ₂₈ H ₂₆ N ₄ OS ₂
281671	4-NO ₂ -Ph	SMe	O	C ₂₈ H ₂₄ N ₆ O ₅ S ₂
281672	CH ₂ CH ₂ Ph	SEt	O	C ₃₄ H ₃₈ N ₄ OS ₂
281675	H	Ph	CH ₂	C ₂₇ H ₂₄ N ₄



Compound	R1	Formula
281673	OMe	C ₂₆ H ₂₄ N ₂ O ₇ S ₂
281674	Me	C ₂₆ H ₂₄ N ₂ O ₅ S ₂

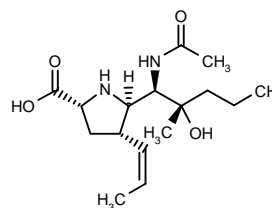
SOURCE – Pharmacia & Upjohn (Pharmacia).

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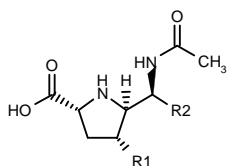
282352

(±)-5(*RS*)-[1(*RS*)-(Acetylamino)-2(*SR*)-hydroxy-2-methyl-pentyl]-4(*SR*)-[1(*Z*)-propenyl]pyrrolidine-2(*RS*)-carboxylic acid

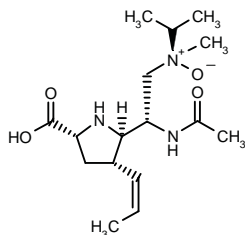


C16 H28 N2 O4; Mol wt: 312.4072

ACTION – Neuraminidase inhibitor reported to inhibit influenza A and influenza B neuraminidase with K_i values between 0.1 nM and 24 μ M and plaque formation of influenza virus A/N2/Tokyo in MDCK cells with EC_{50} values ranging between 1 nM and 1 μ M. Potentially useful in the treatment or prevention of influenza infections. Other representative compounds from this series are:



Compound	R1	R2	Isomer	Formula
282357	CH=CHMe	(S*)-CH(OH)CH ₂ CN	racemic	C ₁₄ H ₂₁ N ₃ O ₄
282358	vinyl	(S*)-CH(OH)Et	racemic	C ₁₃ H ₂₂ N ₂ O ₄
282359	4-thiazolyl	i-Bu	racemic	C ₁₅ H ₂₃ N ₃ O ₃ S
282360	4-imidazolyl	i-Bu	racemic	C ₁₅ H ₂₄ N ₄ O ₃



282355: C₁₆ H₂₉ N₃ O₄

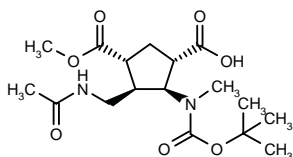
SOURCE – Abbott.

REFERENCES

1. Maring, C.J. et al. (Abbott Laboratories Inc.) *Pyrrolidines as inhibitors of neuraminidases*. WO 9954299.

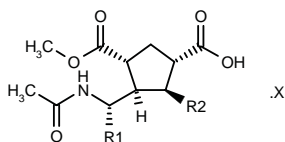
282361

(±)-3(*RS*)-(Acetamidomethyl)-2(*SR*)-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]-4(*RS*)-(methoxycarbonyl)-cyclopentane-1(*SR*)-carboxylic acid

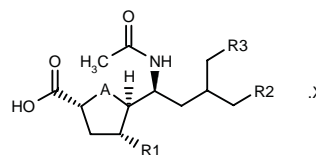


C₁₇ H₂₈ N₂ O₇; Mol wt: 372.4152

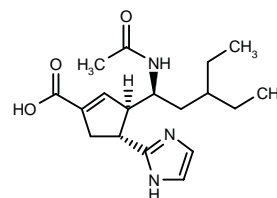
ACTION – Neuraminidase inhibitor reported to inhibit influenza A and influenza B neuraminidase with K_i values between 0.1 nM and 24 μM. Potentially useful in the treatment or prevention of influenza infections. Other representative compounds from this series are:



Compound	R1	R2	X	Isomer	Formula
282362	H	NH ₂	HCl	racemic	C ₁₁ H ₁₈ N ₂ O ₅ ·HCl
282363	CH ₂ CH(Et) ₂	H		racemic	C ₁₇ H ₂₉ NO ₅



Compound	R1	R2=R3	A	X	Isomer	Formula
282364	2-imidazolyl	Me	CH ₂		1R,3R,4R,1'S	C ₁₈ H ₂₉ N ₃ O ₃
282365	4-imidazolyl	H	O	HCl	racemic	C ₁₅ H ₂₃ N ₃ O ₄ ·HCl



282366: C₁₈ H₂₇ N₃ O₃

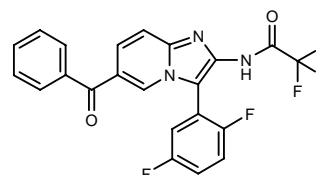
SOURCE – Abbott.

REFERENCES

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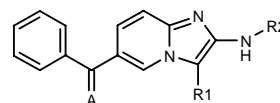
283420

N-[6-Benzoyl-3-(2,5-difluorophenyl)imidazo[1,2-*a*]pyridin-2-yl]-2,2,2-trifluoroacetamide



C₂₂ H₁₂ F₅ N₃ O₂; Mol wt: 445.3458

ACTION – Antiviral agent reported to inhibit the growth of picornaviruses, enteroviruses, *Cardiovirus*, *Aphthovirus* and hepatitis viruses. A representative compound from a series of pyridoimidazole compounds, wherein the following are also included:



Compound	R1	R2	A	Formula
283422	3-CF ₃ O-Ph	COCF ₃	-O-	C ₂₃ H ₁₃ F ₆ N ₃ O ₃
283424	SO ₂ Me	COCF ₃	-O-	C ₁₇ H ₁₂ F ₃ N ₃ O ₄ S
283425	2,5-(F) ₂ -Ph	H	-O-	C ₂₀ H ₁₃ F ₂ N ₃ O
283427	(F)5-Ph	H	-O-	C ₂₀ H ₁₀ F ₅ N ₃ O
283428	1-Naph	H	-N(OH)-	C ₂₄ H ₁₈ N ₄ O
283429	(F)5-Ph	H	-N(OH)-	C ₂₀ H ₁₁ F ₅ N ₄ O
283430	i-PrS	H	-O-	C ₁₇ H ₁₇ N ₃ OS
283431	Ac	H	-CH(CONHMe)-	C ₁₉ H ₁₈ N ₄ O ₂

SOURCE – Lilly.

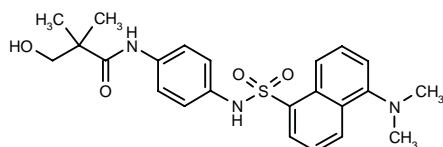
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BAY-38-4766*,1-9

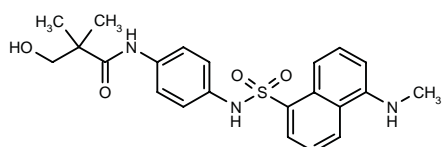
279333

N-[4-[5-(Dimethylamino)-1-naphthylsulfonamido]phenyl]-3-hydroxy-2,2-dimethylpropionamide



C23 H27 N3 O4 S; Mol wt: 441.5493

ACTION – Antiviral agent, a potent and selective, non-nucleosidic inhibitor of human cytomegalovirus (HCMV) replication with good antiviral activity against different HCMV strains (mean $IC_{50} = 1.17 \mu M$) including ganciclovir-resistant strains; it displayed potency about 5-fold greater than ganciclovir. Compound was also found to be active against some monkey CMV strains and showed inhibitory activity against rodent CMV strains. Crossresistance in HCMV and MCMV strains was observed with compounds of the same class, but not with nucleosides such as ganciclovir, cidofovir or foscavir, indicating a different mode of action; compound acts in a unique and different manner relative to the available DNA polymerase inhibitors: it abolished the propagation and spread of CMV by inhibiting the cleavage of polygenomic concatemeric viral DNA, thereby preventing the packaging of unit genome length molecules. In a murine pathogenicity model in which immunodeficient mice were inoculated with MCMV, compound (3-100 mg/kg p.o. b.i.d. for 8 days) showed comparable activity to ganciclovir, prolonging survival and decreasing viral DNA content in liver and spleen. In another *in vivo* model where HCMV was implanted into the abdominal cavity of SCID mice, compound, like ganciclovir, dose-dependently (10-50 mg/kg p.o. b.i.d. for 4 days) decreased HCMV replication. It showed an excellent safety profile and favorable pharmacokinetics in human, with a C_{max} of 1.29 ± 1.74 and 1.94 ± 2.15 mg/l, respectively, and a t_{max} of 0.667-2.5 and 0.667-5.0 h, respectively, after 500 and 1000 mg p.o., as well as a long terminal elimination half-life (13.1-14.4 h at these doses). It is currently undergoing pilot phase II trials for the treatment of patients infected with HCMV. **Bay-43-9695** is the major active metabolite.



Bay-43-9695 [281249]^{4,6,8}: C22 H25 N3 O4 S

SOURCE – Bayer.

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2. Eckenberg, P. et al. *Structure-activity relationships of BAY 38-4766 - A novel nonnucleosidic inhibitor of human cytomegalovirus replication.* 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F940.
3. Hallenberger, S. et al. *Mechanism of antiviral action of BAY 38-4766 - A novel nonnucleosidic inhibitor of human cytomegalovirus replication.* 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F941.
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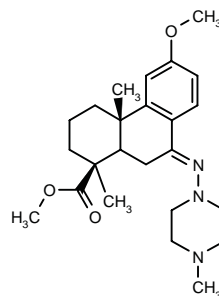
MONOGRAPH – Sorbera, L. et al. *Bay-38-4766.* Drugs Fut 1999, 24(12): 1297.

*Identified compound **279333** (see **279331**) Drug Data Rep 1999, 021(10): 0911.

LY-314177

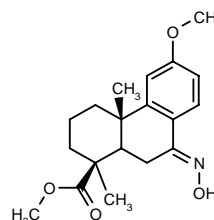
280851

1(*S*),4a(*S*)-Dimethyl-6-methoxy-9-(4-methylpiperazin-1-ylimino)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic acid methyl ester



C24 H35 N3 O3; Mol wt: 413.5585

ACTION – Antiviral agent with excellent activity against influenza A/Kawasaki (H1N1) and influenza A/Ann Arbor (H2N2) viruses ($IC_{50} = 0.08$ and $0.1 \mu g/ml$, respectively). *In vivo*, compound protected mice from influenza A virus infection, giving a 90% survival rate when administered i.p. at 100 mg/kg b.i.d. for 8 days. Another representative compound within this series of podocarpic acid derivatives is:



LY-311912 [280852]: C19 H25 N O4

SOURCE – Lilly.

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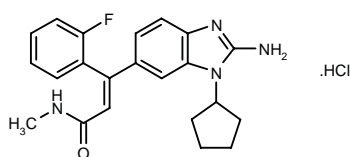
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LY-368177*,1-3

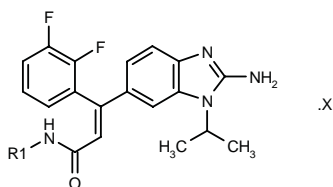
260677

3-(2-Amino-1-cyclopentylbenzimidazol-6-yl)-3-(2-fluorophenyl)-N-methyl-2(Z)-propenamide hydrochloride



C22 H23 F N4 O . HCl; Mol wt: 414.9096

ACTION – Antiviral agent active against rhinoviruses, with comparable potency to enviroxime against human rhinovirus 14 (HRV-14; $IC_{50} = 0.03 \mu\text{g/ml}$) but much more stable to metabolic degradation *in vitro*. In rats, compound exhibited a good pharmacokinetic profile, with an absolute oral bioavailability of 89.4% and C_{max} of 4202 ng/ml. Other compounds within this series of vinyl carboxamide 2-aminobenzimidazoles include the following:



Compound	R1	X	Formula
LY-366094 [255579] ¹⁻³	Me		C ₂₀ H ₂₀ F ₂ N ₄ O
LY-366853 [259917] ^{*,1,3}	H	HCl	C ₁₉ H ₁₈ F ₂ N ₄ O.HCl

SOURCE – Lilly.

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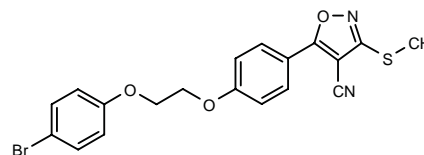
*Identified compound **260677** (see **259917**) Drug Data Rep 1998, 020(04): 0334.

Identified compound **259917 Drug Data Rep 1998, 020(04): 0334.

ON-14

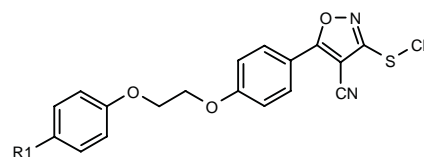
283563

5-[4-[2-(4-Bromophenoxy)ethoxy]phenyl]-3-(methylsulfanyl)isoxazole-4-carbonitrile



C19 H15 Br N2 O3 S; Mol wt: 431.3085

ACTION – Antiviral agent active at noncytotoxic concentrations, particularly against the RNA viruses poliomyelitis virus type 1, ECHO virus type 9, Coxsackievirus B1, rhinovirus and measles virus. It completely inhibited viral replication at concentrations of 0.06-2 μM , with particularly good activity against ECHO 9 and Coxsackievirus B1; CD_{50} values for inhibition of HEP2 and HeLa cell proliferation were 25 and 10 μM , respectively. Other specifically claimed 3-substituted 5-aryl-4-isoxazolecarbonitriles are:



Compound	R1	Formula
ON-11 [283564]	NO2	C ₁₉ H ₁₅ N ₃ O ₅ S
ON-12 [283565]	Me	C ₂₀ H ₁₈ N ₂ O ₃ S
ON-13 [283566]	CO2Et	C ₂₂ H ₂₀ N ₂ O ₅ S

SOURCE – Università degli Studi di Catania, Catania (IT).

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RC-183

281489

Protein of 10,425 Da purified from the edible mushroom Rozites caperata, composed of a peptide (12- or 13-mer) coupled to ubiquitin via an isopeptide bond between the C-terminal glycine of ubiquitin and the ε amino group of a lysine residue in the peptide

ACTION – Antiviral agent, a protein extracted from the edible mushroom *Rozites caperata* proven to inhibit herpes simplex virus type 1 and 2 (HSV-1 and HSV-2) replication in Vero cells with an IC_{50} value of 5 μM or less, with comparable activity to aciclovir ($IC_{50} = 4.5 \mu\text{M}$). At a concentration of 3 $\mu\text{g/ml}$, it also showed antiviral activity against varicella-zoster virus, influenza A/Shanghai (H3N2) virus and respiratory syncytial virus (RSV), but not against adenovirus type VI, HIV or Coxsackievirus A9 and B5. *In vivo* in a model of HSV-1 keratitis in mice, compound significantly reduced the severity of ocular disease when applied topically at a concentration of 1%.

SOURCE – University of Wisconsin-Madison, Madison, WI (US).

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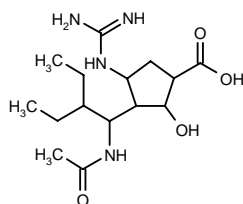
1. Piraino, F. and Brandt, C.R. *Isolation and partial characterization of an antiviral RC-183, from the edible mushroom Rozites caperata*. *Antivir Res* 1999, 43(2): 67.

RWJ-270201¹⁻¹⁰

273549

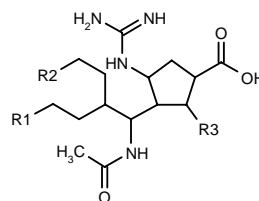
3-(1-Acetamido-2-ethylbutyl)-4-guanidino-2-hydroxy-cyclopentanecarboxylic acid

BCX-1812



C₁₅ H₂₈ N₄ O₄; Mol wt: 328.4102

ACTION – Antiviral agent, a neuraminidase inhibitor active against both established laboratory strains and recent clinical isolates of influenza A virus (H1N1: EC₅₀ < 1 μM; H3N2: EC₅₀ 0.06-16 μM; and H5N1: EC₅₀ < 0.04 μM for inhibition of viral cytopathic effect in MDCK cells), as well as influenza B virus (EC₅₀ = 0.1-83 μM). Compound demonstrated excellent selectivity for influenza neuraminidase when compared to neuraminidases from mammals, bacteria or other viruses. RWJ-270201 was effective in various murine influenza models after oral administration, with at least comparable activity to GS-4104, the ethyl ester prodrug of GS-4071. In mice, following oral administration at a dose of 1 mg/kg/day for 5 days starting 4 h prior to influenza A virus infection, it protected against lethality and weight loss, and delayed treatment (10 mg/kg/day) starting at 24 h postinfection also provided significant protection; if treatment was delayed until 48 h postinfection, however, no significant effect was observed. In another study, compound afforded significant protection against lethal infections in mice caused by influenza A H1N1 and H3N2 and influenza B viruses (1-10 mg/kg/day p.o. b.i.d. for 5 days), and treatment could be delayed up to 60 h postinfection. In addition to preventing death, the treatment reduced lung consolidation and lung virus titers and reversed the decline in arterial oxygen saturation in these models. No acute or subacute toxicity was observed in mice or rats at doses of up to 3000 mg/kg. Currently in phase II trials. Other related neuraminidase inhibitors are:



Compound	R1	R2	R3	Formula
BCX-1827 [273550] ^{1,4,7,10}	H	H	H	C ₁₅ H ₂₈ N ₄ O ₃
BCX-1898 [273551] ^{1,4,7,10}	Me	Me	H	C ₁₇ H ₃₂ N ₄ O ₃
BCX-1823 [273552] ^{1,4,7,10}	Me	Me	OH	C ₁₇ H ₃₂ N ₄ O ₄

SOURCES – BioCryst; R.W. Johnson.

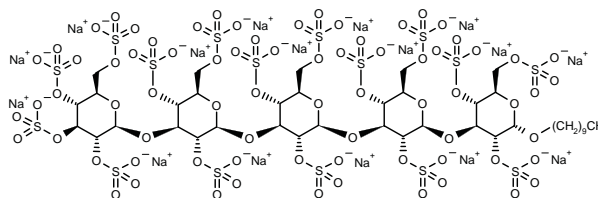
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AIDS MEDICINES

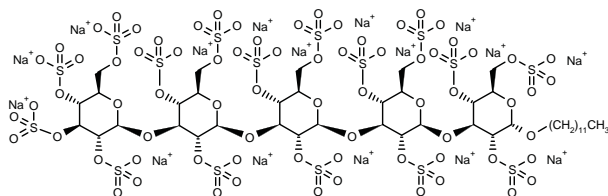
278911

Decyl *O*-(2,3,4,6-tetra-*O*-sulfo-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-sulfo-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-sulfo-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-sulfo-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-sulfo-β-D-glucopyranoside hexadecasodium salt



C₄₀ H₅₆ Na₁₆ O₇₄ S₁₆; Mol wt: 2601.7040

ACTION – Anti-HIV agent, a sulfated laminara-oligosaccharide glycoside proven to inhibit HIV-1 replication in MT-4 cells with an IC_{50} of 0.18 $\mu\text{g/ml}$ and low cytotoxicity ($CC_{50} > 1000 \mu\text{g/ml}$ in uninfected MT-4 cells). Another representative laminara pentaoside is:



278912: C42 H60 Na16 O74 S16

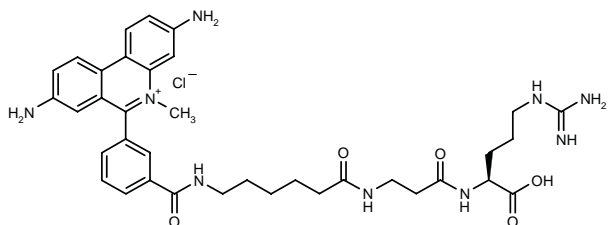
SOURCE – University of Tokyo, Tokyo (JP).

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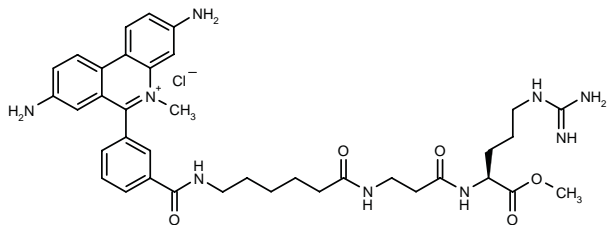
281385

6-[3-[19-Amino-14(S)-carboxy-19-imino-8,12-dioxo-2,9,13,18-tetraazanonadecanoyl]phenyl]-3,8-diamino-5-methylphenanthridinium chloride



C36 H46 Cl N9 O5; Mol wt: 720.2704

ACTION – Anti-HIV agent, an ethidium-arginine conjugate directed against the TAR (transactivation-responsive element) RNA of HIV-1. It inhibited viral replication in infected CEM-SS cells, MT-4 cells and peripheral blood mononuclear cells with respective IC_{50} values of 2.4, 11 and 2.5 μM , without apparent cellular toxicity at up to 100 μM . Compound appears to bind strongly to TAR *in vitro* at both RNA-binding sites. Another related compound is:



281386: C37 H48 Cl N9 O5

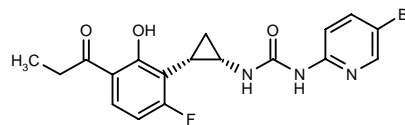
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281389

(+)- N^1 -(5-Bromo-2-pyridinyl)- N^2 -[(1*S*,2*S*)-2-(6-fluoro-2-hydroxy-3-propionylphenyl)cyclopropyl]urea



C18 H17 Br F N3 O3; Mol wt: 422.2523

M.p. 198-9 °C; $[\alpha]_D^{22} +149.8^\circ$ (*c* 0.005, CH_2Cl_2)

ACTION – Anti-HIV agent, an inhibitor of both wild-type ($IC_{50} = 4.8 \text{ nM}$) and mutant (Ile100, Cys181 and Asn103: $IC_{50} = 14, 10$ and 41 nM , respectively) reverse transcriptase. Compound showed antiviral activity in MT-4 cells infected with both wild-type HIV-1 and virus containing the Ile100, Cys181 or Asn103 mutation ($ED_{50} = 12, 53, 95$ and 358 nM , respectively). It showed superior activity to nevirapine and delavirdine against enzyme and HIV-1 replication in MT-4 cells, whereas similar activity to DMP-266 and HBY-097 was observed. Preliminary pharmacokinetic studies in rats demonstrated that compound is orally bioavailable and showed good penetration into the brain, reaching levels comparable to plasma concentrations (1.2 $\mu\text{g/ml}$ in plasma and 5 $\mu\text{g/g}$ in brain at 18.5 min after i.v. administration of 13 mg/kg).

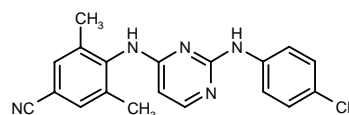
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2. Högberg, M. et al. *Urea-PETT compounds as a new class of HIV-1 reverse transcriptase inhibitors.3.Synthesis and further structure-activity relationship studies of PETT analogues.* J Med Chem 1999, 42(20): 4150.

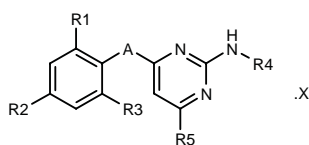
281551

4-[2-(4-Cyanophenylamino)pyrimidin-4-ylamino]-3,5-dimethylbenzonitrile



C20 H16 N6; Mol wt: 340.3884

ACTION – Antiviral agent for AIDS with potent anti-HIV-1 activity in infected MT-4 cells ($IC_{50} = 0.0004 \mu\text{M}$) and low cytotoxicity in uninfected cells ($CC_{50} = 4.7 \mu\text{M}$; selectivity index = 11,632). Compound is reported to be active against HIV-1 strains that have become resistant to known non-nucleoside reverse transcriptase inhibitors. It is also reported to have little or no binding affinity for human α_1 -acid glycoprotein. Within this series of substituted pyrimidine derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	A	X	Formula
281552	Cl	H	Cl	4-CN-Ph	NH ₂	CH ₂		C ₁₈ H ₁₃ Cl ₂ N ₅
281553	Me	Me	Me	4-CN-Ph	H	NH	HCl	C ₂₀ H ₁₉ N ₅ ·HCl
281554	Cl	H	Cl	4-CN-Ph	H	S		C ₁₇ H ₁₀ Cl ₂ N ₄ S
281555	Br	Br	F	4-CN-Ph	H	NH		C ₁₇ H ₁₀ Br ₂ N ₅
281556	Me	CN	Me	4-CN-Ph	H	O		C ₂₀ H ₁₅ N ₅ O
281557	Me	Me	Me	H	4-CN-PhNH	NH		C ₂₀ H ₂₀ N ₆

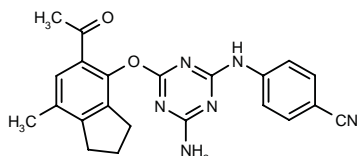
SOURCE – Janssen.

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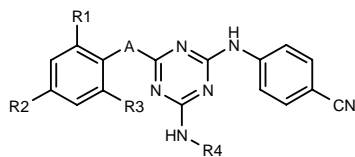
281558

4-[4-(5-Acetyl-7-methylindan-4-yloxy)-6-amino-1,3,5-triazin-2-ylamino]benzonitrile



C₂₂ H₂₀ N₆ O₂; Mol wt: 400.4400

ACTION – Antiviral agent for AIDS with potent anti-HIV-1 activity in infected MT-4 cells (IC₅₀ = 0.001 μM) and low cytotoxicity in uninfected cells (CC₅₀ = 54.1 μM; selectivity index = 45,129). Compound is reported to be active against HIV-1 strains that have become resistant to known non-nucleoside reverse transcriptase inhibitors. It is also reported to have little or no binding affinity for human α₁-acid glycoprotein. Within this series of trisubstituted 1,3,5-triazine derivatives, the following are also included:



Compound	R1	R2	R3	R4	A	Formula
281559	Me	Me	Me	H	-NH-	C ₁₉ H ₁₉ N ₇
281560	Me	Me	Me	OH	-NH-	C ₁₈ H ₁₆ ClN ₇ O
281561	Cl	Cl	Cl	H	-NHNH-	C ₁₆ H ₁₁ Cl ₃ N ₈
281562	Cl	Cl	Cl	OH	-NH-	C ₁₆ H ₁₀ Cl ₃ N ₇ O
281563	Cl	Cl	Me	H	-O-	C ₁₇ H ₁₂ Cl ₂ N ₆ O
281564	Me	Ac	Me	H	-O-	C ₂₀ H ₁₈ N ₆ O ₂
281565	Me	Br	Me	H	-O-	C ₁₈ H ₁₅ BrN ₆ O
281566	Cl	Me	Me	H	-NH-	C ₁₈ H ₁₆ ClN ₇
281567	Br	Me	Br	H	-NH-	C ₁₇ H ₁₃ Br ₂ N ₇

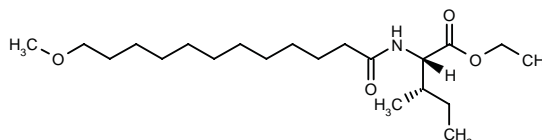
SOURCE – Janssen.

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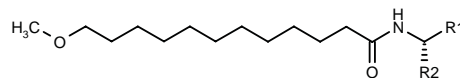
281646

N-(12-Methoxydodecanoyl)-L-isoleucine ethyl ester



C₂₁ H₄₁ N O₄; Mol wt: 371.5579

ACTION – Antiviral agent that inhibits lentiviruses, particularly HIV, and is believed to act as a substrate for *N*-myristoyltransferase (NMT) and/or its acyl coenzyme. The compound was shown to inhibit HIV-1 in syncytium-sensitive Leu-3a-positive CEM cells (EC₅₀ < 2.7 μM). Other compounds from this series of fatty acid analogues and prodrugs include the following:



Compound	R1	R2	Formula
281651	Ph	H	C ₂₀ H ₃₃ NO ₂
281652	CH ₂ Ph	H	C ₂₁ H ₃₅ NO ₂
281653	CH ₂ CO ₂ Et	H	C ₁₈ H ₃₅ NO ₄
281654	CH(Me)CO ₂ Et	H	C ₁₉ H ₃₇ NO ₄
281655	(R)-CH(Me)CO ₂ Et	H	C ₁₉ H ₃₇ NO ₄
281656	CH(CH ₂ Ph)CO ₂ Et	H	C ₂₅ H ₄₁ NO ₄
281657	CO ₂ Et	CH ₂ Ph	C ₂₄ H ₃₉ NO ₄

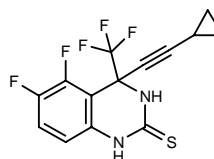
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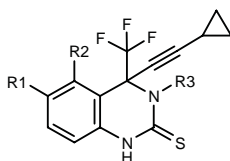
281681

(±)-4-(2-Cyclopropylethynyl)-5,6-difluoro-4-(trifluoromethyl)-1,2,3,4-tetrahydroquinazoline-2-thione



C₁₄ H₉ F₅ N₂ S; Mol wt: 332.2951

ACTION – Antiviral agent for AIDS, an inhibitor of HIV reverse transcriptase. Within this series of 4,4-disubstituted-3,4-dihydroquinazoline-2(1*H*)-thione derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	Formula
281682	Cl	H	H	C ₁₄ H ₁₀ ClF ₃ N ₂ S
281683	F	F	Me	C ₁₅ H ₁₁ F ₃ N ₂ S
281684	Cl	H	Me	C ₁₅ H ₁₂ ClF ₃ N ₂ S

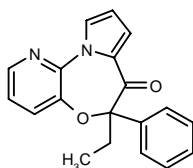
SOURCE – DuPont Pharmaceuticals.

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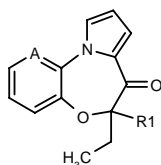
281764

6-Ethyl-6-phenylpyrido[3,2-*b*]pyrrolo[1,2-*d*][1,4]oxazepin-7(6*H*)-one



C₁₉ H₁₆ N₂ O₂; Mol wt: 304.3474

ACTION – Anti-HIV-1 agent, an inhibitor of HIV-1 reverse transcriptase (RT) proven active against both wild-type ($K_i = 0.022 \mu\text{M}$) and clinically relevant mutant RT enzymes containing the single amino acid substitutions L1001, K103N, V106A, Y181I and Y188L ($K_i = 0.04, 0.3, 0.07, 4$ and $1.5 \mu\text{M}$, respectively). Compound showed antiviral activity in HIV-1-infected CEM-SS cells and C8166 cells ($\text{EC}_{50} = 0.069$ and $0.054 \mu\text{M}$, respectively), with low cytotoxicity ($\text{IC}_{50} = 3.9$ and $6 \mu\text{M}$, respectively). It had synergistic anti-HIV-1 activity when tested in combination with zidovudine. Rapid absorption was observed after oral administration of a solutoin (20 mg/kg) to mice, although mean C_{max} and AUC values were significantly lower than after s.c. dosing, and it showed good brain penetration. Within this series of pyrrolobenzoxazepinone derivatives, the following are also included:



Compound	R1	A	Formula
281761	3-MeO-Ph	CH	C ₂₁ H ₁₉ NO ₃
281762	3-Me-Ph	CH	C ₂₁ H ₁₉ NO ₂
281763	2-thienyl	CH	C ₁₈ H ₁₅ N ₂ O ₂ S
281766	2-thienyl	N	C ₁₇ H ₁₄ N ₂ O ₂ S

SOURCE – Istituto di Richerche Farmacologiche Mario Negri, Milano (IT).

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283102

Polynucleotide comprising portions of the genomes of caprine arthritis-encephalitis virus (CAEV) and HIV-1

ACTION – Chimeric CAEV (caprine arthritis-encephalitis virus)/HIV-1 retrovirus (CHIV) vaccine which has the core of CAEV and the immunogenicity of HIV-1. The retroviral genome includes the regulatory sequences from CAEV along with such other CAEV coding sequences as required to render the CHIV nonpathogenic, as well as an HIV-1 *env* gene. The CHIV immunogen is capable of stimulating an immune response against HIV-1 for increasing resistance to infection in individuals not previously exposed to the virus, or for reducing the severity of HIV-1 disease in infected individuals.

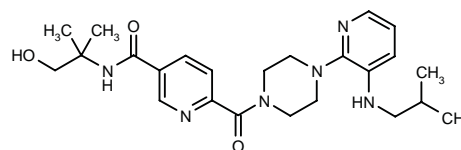
SOURCE – University of Southern California, Los Angeles, CA (US).

REFERENCES

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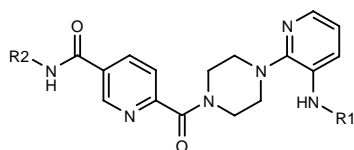
283347

N-(2-Hydroxy-1,1-dimethylethyl)-6-[4-[3-(isobutyl-amino)pyridin-2-yl]piperazin-1-ylcarbonyl]pyridine-3-carboxamide



C₂₄ H₃₄ N₆ O₃; Mol wt: 454.5716

ACTION – Antiviral agent able to inhibit the proliferation of retroviruses such as hepatitis B virus (HBV) and HIV by inhibiting reverse transcriptase (RT) (90 and 62% inhibition of HBV RT and HIV RT, respectively, at $1 \mu\text{g/ml}$). No cytotoxicity was detected in HepG2 cells at concentrations of up to $200 \mu\text{M}$. Other 2,5-pyridinedi-carboxylic acid derivatives are:



Compound	R1	R2	Formula
283349	Et	CH ₂ CH ₂ OH	C ₂₀ H ₂₆ N ₆ O ₃
283350	i-Bu	CH ₂ CH ₂ OH	C ₂₂ H ₃₀ N ₆ O ₃
283351	Et	i-Pr	C ₂₁ H ₂₈ N ₆ O ₂
283352	i-Bu	i-Pr	C ₂₃ H ₃₂ N ₆ O ₂
283354	i-Pr	t-Bu	C ₂₃ H ₃₂ N ₆ O ₂
283356	i-Pr	cyclopropyl	C ₂₂ H ₂₈ N ₆ O ₂
283358	i-Pr	CH ₂ CH(OMe) ₂	C ₂₃ H ₃₂ N ₆ O ₄
283359	i-Pr	1-imidazolyl-(CH ₂) ₃	C ₂₅ H ₃₂ N ₈ O ₂
283360	i-Bu	1-imidazolyl-(CH ₂) ₃	C ₂₆ H ₃₄ N ₈ O ₂
283361	i-Pr	3-OH-2-Pyr	C ₂₄ H ₂₇ N ₇ O ₃

SOURCE – Dong-Wha.

REFERENCES

1. Yoon, S.J. et al. (Dong-Wha Pharmaceuticals Industry Co. Ltd) *Novel 2,5-pyridinedicarboxylic acid derivs.* WO 9958526.

CYANOVIRIN N

238075

11-kDa protein isolated from the cyanobacterium Nostoc ellipsosporum and subsequently recombinantly produced in Escherichia coli, whose sequence is: LGKFSQTCYNSAIQGSVLTSTCERTNGGYNTSSIDLNS-VIENVDSLKWQPSNFIETCRNTNLGSSELAEECKTR-AQQFVSTKINLDDHIANIDGTLKYE (8-22),(58-73)-bis(disulfide)

CV-N

ACTION – Anti-HIV agent, a protein isolated from the cyanobacterium *Nostoc ellipsosporum*, and subsequently produced by recombinant techniques. Compound was able to inactivate diverse primary strains of HIV-1 including M-tropic forms involved in sexual transmission of HIV, as well as T-tropic and dual-tropic forms, HIV-2 and simian immunodeficiency virus (SIV). Compound is directly virucidal, interacting in an unusual manner with the viral envelope, binding with extremely high affinity to the viral surface envelope glycoprotein gp120 in a manner that does not occlude or alter the CD4 binding site or V3 loop or other domains on gp120 recognized by defined MAbs. Compound did not block infectivity of other enveloped nonlentivirus viruses such as herpesvirus type 1 (HSV-1), cytomegalovirus and adenovirus type 5. It was not toxic *in vivo* in a rabbit model of vaginal toxicity/irritancy and it was not cytotoxic *in vitro* to human immune cells and lactobacilli. Potentially useful for topical use to prevent sexual transmission of HIV infection and disease.

SOURCE – National Cancer Institute, Bethesda, MD (US).

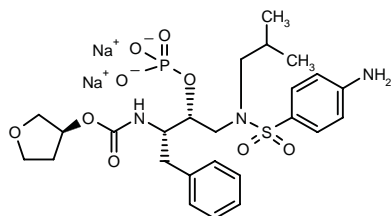
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8. Boyd, M.R. et al. *Discovery of cyanovirin-N, a novel HIV-inactivating protein from Nostoc ellipsosporum that targets viral gp120.* 11th Int Conf AIDS (July 7-12, Vancouver) 1996, Abst Mo.A.1093.
9. Boyd, M.R. et al. *Discovery of cyanovirin-N, a novel human immunodeficiency virus-inactivating protein that binds viral surface envelope glycoprotein gp120: Potential applications to microbicide development.* Antimicrob Agents Chemother 1997, 41(7): 1521.
10. Esser, M.T. et al. *Cyanovirin-N binds to gp120 to interfere with CD4-dependent human immunodeficiency virus type 1 virion binding, fusion, and infectivity but does not affect the CD4 binding site on gp120 or soluble CD4-induced conformational changes in gp120.* J Virol 1999, 73(5): 4360.
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20. *Licensing opportunity from NIH: cyanovirin N-based topical microbicides active against HIV.* DailyDrugNews.com (Daily Essentials) 1999, Oct 13.

GW-433908A**278740**

N-[3-[*N*-(4-Aminophenylsulfonyl)-*N*-isobutylamino]-1(*S*)-benzyl-2(*R*)-(phosphonoxy)propyl]carbamic acid tetrahydrofuran-3(*S*)-yl ester disodium salt

VX-175 (as free acid)



C25 H34 N3 Na2 O9 P S; Mol wt: 629.5756

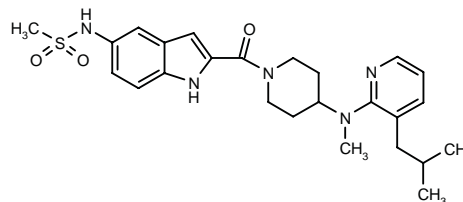
ACTION – Anti-HIV agent, a phosphate ester prodrug of amprenavir⁺ with improved water solubility ranging from 0.3 mg/ml to > 100 mg/ml at pH 7. In rats, compound showed rapid and complete conversion to amprenavir across the gastrointestinal epithelium, giving a 90% relative bioavailability compared to the toxicology formulation of amprenavir. In dogs, it was rapidly converted to amprenavir at or in the intestinal layer and was not itself significantly absorbed, resulting in amprenavir exposure that was 63% of that obtained from an equivalent molar dose of amprenavir in the clinical formulation. The toxicological profile of prodrug in rats and dogs was similar to the parent drug. Currently in phase II trials in HIV-infected patients.

SOURCES – Glaxo Wellcome; Vertex.**REFERENCES**

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7. *Two new drugs added to the R&D pipeline at Glaxo Wellcome*. DailyDrugNews.com (Daily Essentials) 1999, July 16.

⁺Drug Data Rep 1999, 021(07): 0633.**PNU-103657****280505**

N-[2-[4-[*N*-(3-Isobutylpyridin-2-yl)-*N*-methylamino]-piperidin-1-ylcarbonyl]-1*H*-indol-5-yl]methanesulfonamide



C25 H33 N5 O3 S; Mol wt: 483.6337

White solid, m.p. 200-1 °C.

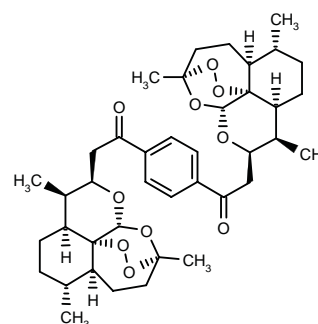
ACTION – Anti-HIV agent, a non-nucleoside reverse transcriptase inhibitor active against wild-type enzyme (IC₅₀ = 0.51 μM) and P236L and Y181C mutants (IC₅₀ = 1.1 and 2.6 μM, respectively), being more active than delavirdine against the mutant enzymes (IC₅₀ = 0.26, 18 and 8.32 μg/ml, respectively). Consistent with its RT-inhibitory activity, compound showed antiviral activity against delavirdine-resistant (P236L) HIV-1 (EC₉₀ = 1.8 μM). *In vitro* metabolism studies showed no improvement in metabolic stability in the presence of hepatic cytochrome P-450 relative to delavirdine and *in vivo* pharmacokinetic studies evidenced higher i.v. clearance than delavirdine. Compound exhibited good oral bioavailability in rats approaching that of delavirdine (64% at a dose of 30.3 mg/kg vs. 64% and 169%, respectively, at delavirdine doses of 15 and 28 mg/kg).

SOURCE – Pharmacia & Upjohn (Pharmacia).**REFERENCES**

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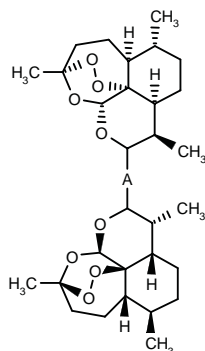
TREATMENT OF PROTOZOAL DISEASES
281734

1,1'-[1,4-Phenylene]bis[2-[(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*R*,12*R*,12*aR*)-3,6,9-trimethyl-3,12-epoxy-12*H*-decahydro-pyrano[4,3-*J*]-1,2-benzodioxepin-10-yl]ethanone]



C40 H54 O10; Mol wt: 694.8566

ACTION – Antimalarial and antineoplastic agent, a derivative of the natural antimalarial artemisinin with superior potency than the parent compound against chloroquine-sensitive *Plasmodium falciparum* NF54 (IC_{50} = 1.9 and 9.7 nM, respectively). Compound also exhibited antiproliferative activity *in vitro* against a panel of human cancer cell lines including leukemia and colon 205 cancer cells, as well as *in vivo* antitumor activity in mice implanted s.c. and i.p. with various human tumor xenografts. Other related artemisinin derivatives are:



Compound	A	Isomer	Formula
281736	-4,6-(MeO)2-1,3-Ph-	10R,10'R	C ₃₈ H ₅₄ O ₁₀
281738	-ethynylene-1,4-Ph-ethynylene-	10S,10'S	C ₄₀ H ₅₀ O ₈

SOURCES – Hauser; Johns Hopkins University, Baltimore, MD (US).

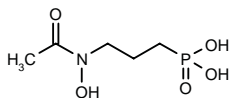
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2. Posner, G.H. et al. *Antimalarial, antiproliferative, and antitumor activities of artemisinin-derived, chemically robust, trioxane dimers*. J Med Chem 1999, 42(21): 4275.

FR-900098

280572

3-(*N*-Acetyl-*N*-hydroxyamino)propylphosphonic acid



C5 H12 N O5 P; Mol wt: 197.1258

ACTION – Antimalarial agent, an orally active fosmidomycin derivative extracted from *Streptomyces rubellomurinus* sp. nov., able to inhibit the growth of multidrug-resistant strains of *Plasmodium falciparum* *in vitro* (IC_{50} = 90-170 nM). It was effective *in vivo* in curing mice infected with the rodent malaria parasite *Plasmodium vinckei*; parasitemia was < 1% in mice treated orally with compound at a dose of 20 mg/kg for 4 days, and animals receiving doses of 50 or 100 mg/kg were apparently parasite-free; total cure was obtained after administration of 30 mg/kg p.o. for 8 days. In comparison, fosmidomycin was slightly less potent than compound *in vitro* (IC_{50} = 290-350 nM against multidrug-resistant *P. falciparum*) but showed similar antimalarial activity *in vivo*. FR-900089 appears to exert its antimalarial activity via a mevalonate-independent

pathway of isoprenoid biosynthesis –the 1-deoxy-D-xylulose 5-phosphate (DOXP) pathway via inhibition of DOXP reductoisomerase.

SOURCE – Fujisawa.

REFERENCES

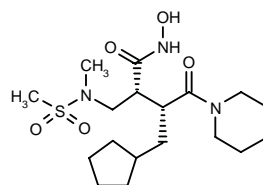
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

281635

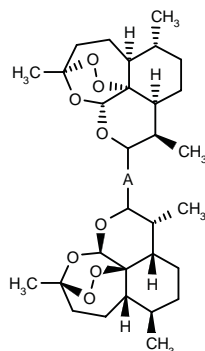
3(*R*)-(Cyclopentylmethyl)-2(*R*)-[*N*-methyl-*N*-(methylsulfonyl)aminomethyl]-4-oxo-4-(1-piperidiny)butyromyxamic acid



C18 H33 N3 O5 S; Mol wt: 403.5407

ACTION – Potent collagenase 1 (MMP-1) inhibitor (IC_{50} = 6 nM) with high selectivity over other matrix metalloproteinases including gelatinase A (MMP-2), stromelysin 1 (MMP-3), collagenase 3 (MMP-13) and collagenase 2 (MMP-8) (IC_{50} = 900, 200, 400 and 200 nM, respectively). Good oral bioavailability was seen in rats, with plasma C_{max} of 171.8 ng/ml. Selected for further pharmacological evaluation as an antiarthritic agent. Another related compound is:

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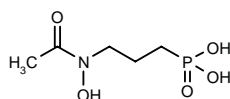
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FR-900098

280572

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C5 H12 N O5 P; Mol wt: 197.1258

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pathway of isoprenoid biosynthesis –the 1-deoxy-D-xylulose 5-phosphate (DOXP) pathway via inhibition of DOXP reductoisomerase.

SOURCE – Fujisawa.

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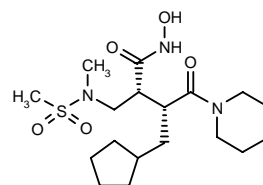
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

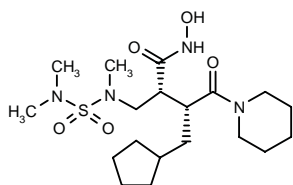
281635

3(R)-(Cyclopentylmethyl)-2(R)-[N-methyl-N-(methylsulfonyl)aminomethyl]-4-oxo-4-(1-piperidinyl)butyroxamic acid



C18 H33 N3 O5 S; Mol wt: 403.5407

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281637: C₁₉ H₃₆ N₄ O₅ S

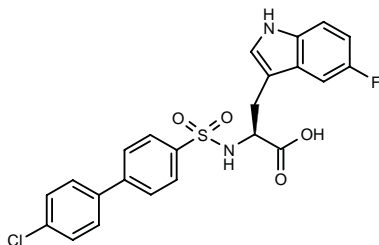
SOURCE – British Biotech.

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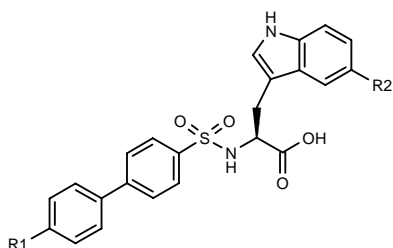
281676

2(*S*)-(4'-Chlorobiphenyl-4-ylsulfonamido)-3-(5-fluoro-1*H*-indol-3-yl)propionic acid



C₂₃ H₁₈ Cl F N₂ O₄ S; Mol wt: 472.9222

ACTION – An inhibitor of matrix metalloproteinases, particularly stromelysin (IC₅₀ = 40 nM) and neutrophil collagenase (IC₅₀ = 80 nM), with potential in the treatment or prophylaxis of a broad range of disorders such as osteoarthritis, rheumatoid arthritis, periodontal diseases, osteoporosis, atherosclerosis and cancer. Other specifically claimed compounds from this series of (*S*)-2-(biphenyl-4-sulfonylamino)-3-(1*H*-indolyl)propionic acid derivatives are:



Compound	R1	R2	Formula
281677	H	F	C ₂₃ H ₁₉ FN ₂ O ₄ S
281678	Cl	OH	C ₂₃ H ₁₉ ClN ₂ O ₅ S
281679	Cl	H	C ₂₃ H ₁₉ ClN ₂ O ₄ S
281680	Cl	OMe	C ₂₄ H ₂₁ ClN ₂ O ₅ S

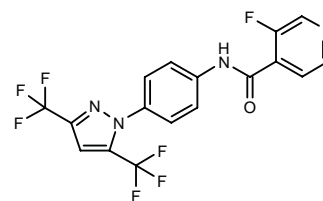
SOURCE – Aventis Pharma.

REFERENCES

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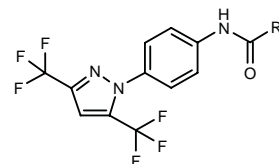
281798

N-[4-[3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl]-3-fluoropyridine-4-carboxamide



C₁₇ H₉ F₇ N₄ O; Mol wt: 418.2711

ACTION – Cytokine production inhibitor shown to inhibit IL-4 and IL-5 secretion in human T-cells with respective IC₅₀ values of 4.8 and 22 nM (IC₅₀ FK-506 [tacrolimus] = 0.7 and 0.5 nM, respectively), and the concanavalin A-stimulated proliferation of human peripheral blood mononuclear cells with an IC₅₀ of 42 nM. Particularly useful for the treatment of rheumatoid arthritis, atopic dermatitis, asthma, psoriasis and graft rejection. Other exemplified pyrazoles include the following:



Compound	R1	Formula
281799	1-cyclohexenyl	C ₁₈ H ₁₅ F ₆ N ₃ O
281800	2,3-(F)2-Ph	C ₁₈ H ₉ F ₂ N ₃ O

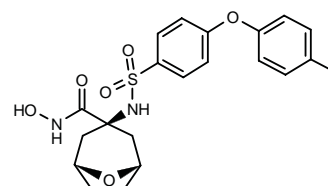
SOURCE – Abbott.

REFERENCES

1. Ba Maung, N.Y. et al. (Abbott Laboratories Inc.) *Pyrazole inhibitors of cytokine production*. WO 9951580.

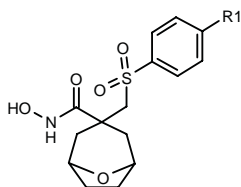
281970

exo-3-[4-(4-Fluorophenoxy)phenylsulfonamido]-8-oxabicyclo[3.2.1]octane-3-carboxylic acid



C₂₀ H₂₁ F N₂ O₆ S; Mol wt: 436.4579

ACTION – An inhibitor of matrix metalloproteinases and TNF- α -converting enzyme (TACE) with potential in the treatment of a broad range of disorders such as osteoarthritis, rheumatoid arthritis, inflammatory bowel disease, emphysema, chronic obstructive pulmonary disease and Alzheimer's disease. Other specifically claimed compounds from this series of bicyclic hydroxamic acid derivatives include the following:



Compound	R1	Isomer	Formula
281971	4-F-PhO	exo	C ₂₁ H ₂₂ FNO ₆ S
281972	OPh		C ₂₁ H ₂₃ NO ₆ S
281973	4-F-Ph	exo	C ₂₁ H ₂₂ FNO ₅ S
281974	4-Cl-PhO	exo	C ₂₁ H ₂₂ ClNO ₆ S

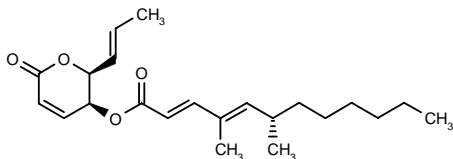
SOURCE – Pfizer.

REFERENCES

1. Robinson, R.P. (Pfizer Products Inc.) *Bicyclic hydroxamic acid derivs.* WO 9952910.

282016

4,6(*S*)-Dimethyl-2(*E*),4(*E*)-dodecadienoic acid 6-oxo-2(*S*)-[1(*E*)-propenyl]-3,6-dihydro-2*H*-pyran-3(*S*)-yl ester



C22 H32 O4; Mol wt: 360.4908

ACTION – Antiinflammatory agent shown to inhibit lipopolysaccharide (LPS)-induced cytokine production, an ester of the antifungal metabolite phomalactone extracted from fermentations of the coelomycete *Phomopsis* sp. It is able to inhibit both LPS-induced TNF- α production in U937 cells (IC₅₀ = 0.08 μ M) and LPS-induced IL-1 β production in peripheral blood mononuclear cells (PBMCs; IC₅₀ = 0.19 μ M); in PBMCs, the effect against IL- β was selective relative to TNF- α , and the inhibitory effect on IL-1 β production appeared to involve a posttranslational mechanism. Potentially useful for the treatment of conditions such as Crohn's disease, multiple sclerosis and rheumatoid arthritis.

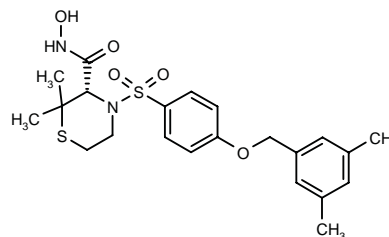
SOURCES – TerraGen; Xenova.

REFERENCES

1. Wrigley, S.K. et al. (Xenova Group plc) *Cytokine production inhibitors.* WO 9817661.
2. Wrigley, S.K. et al. *A novel (6S)-4,6-dimethyldodeca-2E,4E-dienoyl ester of phomalactone and related α -pyrone esters from a Phomopsis sp. with cytokine production inhibitory activity.* J Antibiot 1999, 52(10): 862.

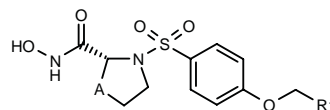
283298

4-[4-(3,5-Dimethylbenzyloxy)phenylsulfonyl]-2,2-dimethylthiomorpholine-3(*S*)-carboxydroxamic acid



C22 H28 N2 O5 S2; Mol wt: 464.6042

ACTION – Matrix metalloproteinase (MMP) inhibitor that selectively inhibits the production of soluble TNF- α . Potentially useful for the treatment of inflammatory disorders and autoimmune diseases, among other disorders. Other specifically claimed substituted hydroxamic acids include the following:



Compound	R1	A	Formula
283299	2,6-(CF ₃) ₂ -4-Pyr	-C(Me) ₂ S-	C ₂₁ H ₂₁ F ₆ N ₃ O ₅ S ₂
283300	2-Me-4-quinoliny	-C(Me) ₂ S-	C ₂₄ H ₂₇ N ₃ O ₅ S ₂
283301	2-EtO-4-quinoliny	-C(Me) ₂ S-	C ₂₅ H ₂₉ N ₃ O ₆ S ₂
283302	3,5-(CF ₃) ₂ -Ph	-CH ₂ -	C ₂₀ H ₁₈ F ₆ N ₂ O ₅ S
283303	3-Me-4-quinoliny	-C(Me) ₂ S-	C ₂₄ H ₂₇ N ₃ O ₅ S ₂
283304	3-Cl-4-quinoliny	-C(Me) ₂ S-	C ₂₃ H ₂₄ ClN ₃ O ₅ S ₂

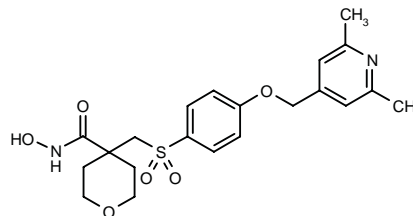
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Voss, M.E. et al. (DuPont Pharmaceuticals Co.) *Novel substd. aryl hydroxamic acids as metalloproteinase inhibitors.* WO 9958531.

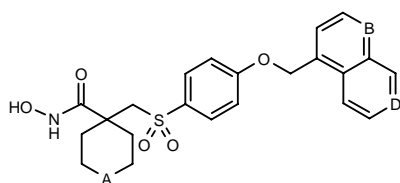
283305

4-[4-(2,6-Dimethylpyridin-4-ylmethoxy)phenylsulfonyl-methyl]tetrahydropyran-4-carboxydroxamic acid



C21 H26 N2 O6 S; Mol wt: 434.5104

ACTION – Matrix metalloproteinase (MMP) inhibitor, particularly MMPs that process TNF- α , i.e., TNF- α convertase. It reduces TNF- α levels without inhibiting MMP-1 (fibroblast collagenase), MMP-2 (gelatinase A) or MMP-9 (gelatinase B), and is thus expected to be associated with reduced side effects. Potentially useful in the treatment of inflammatory diseases including rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, multiple sclerosis, neurodegenerative diseases, psoriasis, autoimmune diseases, Crohn's disease, inflammatory bowel disease, as well as HIV infection, fever, cachexia, shock, graft-versus-host reaction and tumor growth or metastasis. Other specifically claimed substituted aryl hydroxamic acids include the following:



Compound	A	B	D	Formula
283306	-O-	N	CH	C ₂₃ H ₂₄ N ₂ O ₆ S
283307	-NH-	N	CH	C ₂₃ H ₂₅ N ₃ O ₅ S
283308	-N(SO ₂ Me)-	CH	N	C ₂₄ H ₂₇ N ₃ O ₇ S ₂
283309	-N(CO ₂ Me)-	N	CH	C ₂₅ H ₂₇ N ₃ O ₇ S
283310	-N(CO-cyclopropyl)-	CH	N	C ₂₇ H ₂₉ N ₃ O ₆ S

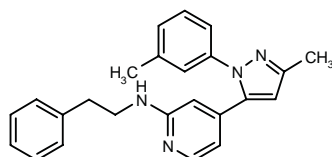
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Xue, C.-B. et al. (DuPont Pharmaceuticals Co.) *Subst. aryl hydroxamic acids as metalloproteinase inhibitors*. WO 9958528.

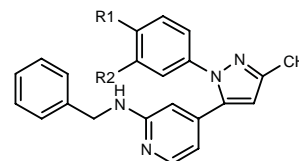
283353

N-[4-[3-Methyl-1-(3-methylphenyl)-1*H*-pyrazol-5-yl]-pyridin-2-yl]-*N*-(2-phenylethyl)amine



C₂₄ H₂₄ N₄; Mol wt: 368.4816

ACTION – p38 MAP kinase inhibitor shown to inhibit human p38 MAP kinase α with an IC₅₀ value of < 0.01 μ M and lipopolysaccharide-stimulated TNF- α production in human peripheral blood mononuclear cells or human histiocytic lymphoma U937 cells with IC₅₀s of 0.02-0.05 μ M. As such, it is considered to be useful for the treatment of fever and inflammation, i.e., rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, adult respiratory distress syndrome, pulmonary sarcoidosis and asthma, as well as viral and bacterial infections including sepsis, septic shock and AIDS. Other exemplified 1,5-diaryl-substituted pyrazoles are:



Compound	R1	R2	Formula
283355	Cl	H	C ₂₂ H ₁₉ ClN ₄
283357	H	Me	C ₂₃ H ₂₂ N ₄

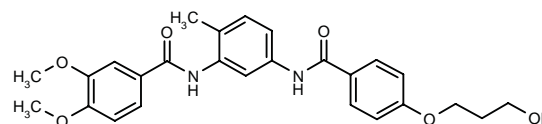
SOURCE – Searle (Pharmacia).

REFERENCES

1. Weier, R.M. et al. (G.D. Searle & Co.) *1,5-Diaryl subst. pyrazoles as p38 kinase inhibitors*. WO 9958523.

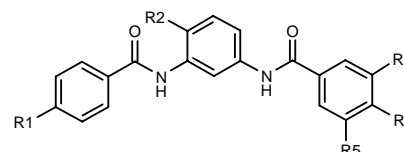
283362

N-[5-[4-(3-Hydroxypropoxy)benzamido]-2-methylphenyl]-3,4-dimethoxybenzamide

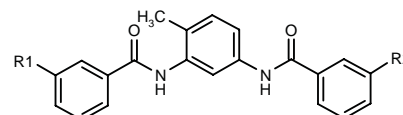


C₂₆ H₂₈ N₂ O₆; Mol wt: 464.5152

ACTION – Inhibitor of the production of cytokines such as TNF- α , IL-1, IL-6 and IL-8 that is believed to act via inhibition of p38 MAP kinase. Potentially useful in the treatment of rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, ischemic heart disease or psoriasis. Other specifically claimed benzamide derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
283363	1-imidazolyl-CH ₂ CH ₂ O	Cl	H	CN	H	C ₂₆ H ₂₀ ClN ₅ O ₃
283367	4-Me-1-Piz-(CH ₂) ₃ O	Me	4-morpholinyl	H	H	C ₃₃ H ₄₁ N ₅ O ₄
283370	2-Pyr-CH ₂ O	Me	4-morpholinyl	H	H	C ₃₁ H ₃₀ N ₄ O ₄
283373	CH ₂ N(Et) ₂	Me	1-pyrrolidinyl	H	F	C ₃₀ H ₃₅ FN ₄ O ₂



Compound	R1	R2	Formula
283365	OCH ₂ CH ₂ N(Et) ₂	4-morpholinyl	C ₃₁ H ₃₈ N ₄ O ₄
283369	4-Pip-O	1-Pip	C ₃₁ H ₃₆ N ₄ O ₃

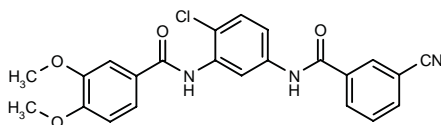
SOURCE – AstraZeneca.

REFERENCES

1. Brown, D.S. and Brown, G.R. (Zeneca Ltd.) *Benzamide derivs. for the treatment of diseases mediated by cytokines*. WO 9959959.

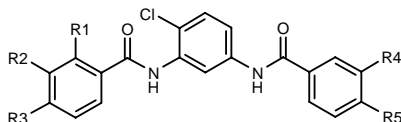
283398

N-[2-Chloro-5-(3-cyanobenzamido)phenyl]-3,4-dimethoxybenzamide



C23 H18 Cl N3 O4; Mol wt: 435.8652

ACTION – Inhibitor of the production of cytokines such as TNF- α , IL-1, IL-6 and IL-8 that is believed to act via inhibition of p38 MAP kinase. Potentially useful in the treatment of rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, ischemic heart disease or psoriasis. Other specifically claimed benzamide derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
283400	H	OMe	OMe	N(Me)2	H	C ₂₄ H ₂₄ ClN ₃ O ₄
283401	H	OMe	OMe	H	CN	C ₂₃ H ₁₈ ClN ₃ O ₄
283403	H	4-Me-1-Piz	H	H	CN	C ₂₆ H ₂₄ ClN ₃ O ₂
283404	H	OMe	OMe	H	H	C ₂₂ H ₁₉ ClN ₂ O ₄
283406	H	OMe	OMe	4-morpholinyl	H	C ₂₆ H ₂₆ ClN ₃ O ₅
283408	H	H	CN	H	OAc	C ₂₃ H ₁₆ ClN ₃ O ₄
283410	NH2	H	OMe	H	H	C ₂₁ H ₁₈ ClN ₃ O ₃
283412	H	H	CN	4-morpholinyl	H	C ₂₆ H ₂₁ ClN ₄ O ₃

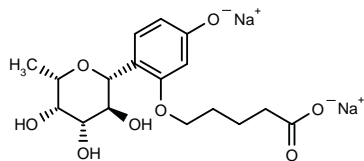
SOURCE – AstraZeneca.

REFERENCES

1. Brown, D.S. and Brown, G.R. (Zeneca Ltd.) *Benzamide derivs. for the treatment of diseases mediated by cytokines*. WO 9959960.

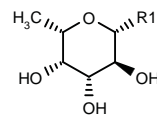
283434

5-[2-(6-Deoxy- β -L-galactopyranosyl)-5-hydroxyphenoxy]-pentanoic acid disodium salt



C17 H22 Na2 O8; Mol wt: 400.3328

ACTION – Selectin inhibitor considered to have potential in the treatment or prevention of inflammatory disorders including rheumatoid arthritis, psoriasis, ulcerative colitis, asthma and atopic dermatitis, ischemia–reperfusion injury, autoimmune diseases and cancer metastasis. Other exemplified acyl-C-glycoside derivatives are:



Compound	R1	Formula
283435	2-[(CH ₂) ₄ CO ₂ Na]-6-(CO ₂ Na)-1-Naph	C ₂₂ H ₂₄ Na ₂ O ₉
283436	2-[(CH ₂) ₅ CO ₂ Na]-6-(CO ₂ Na)-1-Naph	C ₂₃ H ₂₆ Na ₂ O ₉
283437	2-[(CH ₂) ₄ CO ₂ Na]-6-[(CH ₂) ₆ CO ₂ Na]-1-Naph	C ₂₈ H ₃₆ Na ₂ O ₁₀
283438	2-[(CH ₂) ₄ CO ₂ Na]-4-(NaO)-Ph	C ₁₈ H ₂₄ Na ₂ O ₈

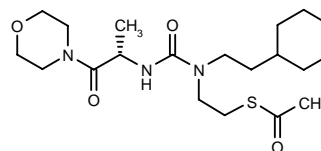
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Ito, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Aryl-C-glycoside derivs.* JP 99269162.

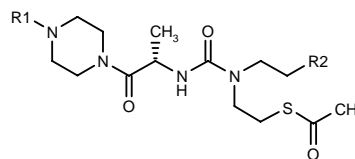
283467

Thioacetic acid *S*-[2-[1-(2-cyclohexylethyl)-3-[1(*S*)-methyl-2-(4-morpholinyl)-2-oxoethyl]ureido]ethyl] ester



C20 H35 N3 O4 S; Mol wt: 413.5795

ACTION – TNF- α production inhibitor, as demonstrated both *in vitro* and *in vivo*. It inhibited lipopolysaccharide-stimulated TNF- α production in rats by 93.5% when given at a dose of 50 mg/kg p.o. As such, this compound is expected to be useful in the treatment of autoimmune diseases such as chronic rheumatoid arthritis. Other exemplified urea derivatives include the following:



Compound	R1	R2	Formula
283468	Me	cyclohexyl	C ₂₁ H ₃₈ N ₄ O ₃ S
283469	H	cyclohexyl	C ₂₀ H ₃₆ N ₄ O ₃ S
283470	Me	cyclopentyl	C ₂₀ H ₃₆ N ₄ O ₃ S

SOURCE – Santen.

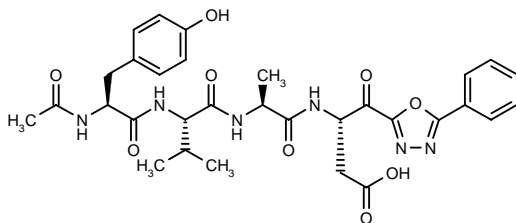
REFERENCES

1. Mita, S. et al. (Santen Pharmaceutical Co., Ltd.) *Novel urea derivs.* WO 9950238.

CQ-0010

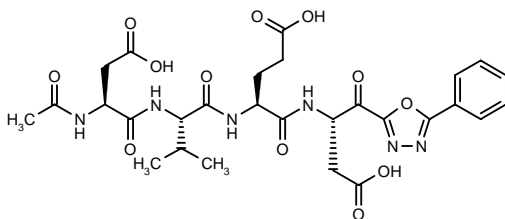
282321

2-(Acetyl-L-tyrosyl-L-valyl-L-alanyl-L-aspartyl)-5-phenyl-1,3,4-oxadiazole



C31 H36 N6 O9; Mol wt: 636.6584

ACTION – Cysteine protease inhibitor with relatively low molecular weight, high potency, reversible inhibition and selectivity with respect to various cysteine proteases. It inhibits caspases such as caspase 8 (FLICE or Mch5), caspase 1 (IL-1 β -converting enzyme or ICE) and caspase 3 (YAMA or CPP32), with respective IC₅₀ values of 0.02, 0.3 and 3.3 μ M. CQ-0010 was an extremely potent and selective inhibitor of IL-1 β production, with an IC₅₀ value of 0.3-0.5 μ M in THP-1 cells and human whole blood, while having no effect against TNF- α production. Potentially useful in the treatment of inflammation, diabetes, septic shock, rheumatoid arthritis and Alzheimer's disease, among others. Another compound from this series of cysteine protease inhibitors is:



CQ-0011 [282322]: C28 H34 N6 O12

SOURCE – Cortech.

REFERENCES

1. Spruce, L.W. et al. (Cortech, Inc.) *Cysteine protease inhibitors*. US 6004933, WO 9954317.

ISIS-18669

283041

Phosphorothioate oligodeoxynucleotide whose sequence is: 5'-GCAGGGCTCGCAGATGGT-3'

ACTION – Antisense phosphorothioate oligodeoxynucleotide that specifically hybridizes with nucleic acids encoding human CD40 and modulates its expression. It was shown to inhibit CD40 mRNA levels by 34% at a concentration of 150 nM. Potentially useful for the treatment of immune-associated, inflammatory or hyperproliferative disorders, i.e., graft-versus-host disease, allograft rejection, autoimmune diseases, asthma, rheumatoid arthritis, inflammatory bowel disease, psoriasis and cancer. Other exemplified oligonucleotides are:

Phosphorothioate oligodeoxynucleotide whose sequence is: 5'-CCAGGCGGCAGGACCACT-3'

283042

Phosphorothioate oligodeoxynucleotide whose sequence is: 5'-GACCAGGCGGCAGGACCA-3'

283043

Phosphorothioate oligodeoxynucleotide whose sequence is: 5'-GGTCAGCAAGCAGCCCCA-3'

283044

Phosphorothioate oligodeoxynucleotide whose sequence is: 5'-AACTGCCTGTTTGCCAC-3'

283045

SOURCE – Isis Pharmaceuticals.

REFERENCES

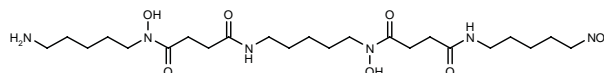
1. Bennett, C.F. and Cowser, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of CD40 expression*. WO 9957320.

IMMUNOMODULATING AGENTS

IC-202B

281037

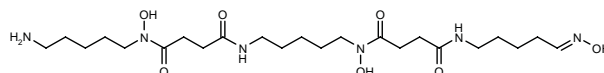
*N*¹-(5-Aminopentyl)-*N*¹-hydroxy-*N*⁴-[5-[*N*-hydroxy-3-[*N*-(5-nitropentyl)carbamoyl]propionamido]pentyl]succinamide



C23 H44 N6 O8; Mol wt: 532.6346

M.p. 117-9 °C.

ACTION – Immunosuppressant isolated from the culture filtrate of *Streptoalloteichus* sp. 1454-19, whose immunosuppressive activity was determined in a mixed lymphocyte culture reaction (IC₅₀ = 1.6 μ g/ml) and against mitogen-induced lymphocyte blastogenesis (IC₅₀ = 2.5 and 4.4 μ g/ml, respectively, against concanavalin A and lipopolysaccharide). Another compound isolated from this source is:



IC-202C [281038]: C23 H44 N6 O7

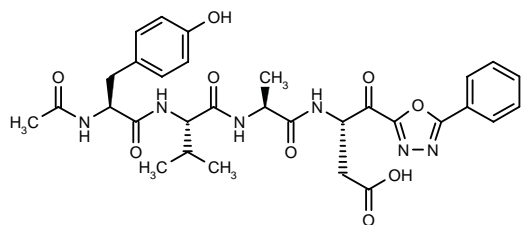
SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

1. Iijima, M. et al. *IC202B and C, new siderophores with immunosuppressive activity produced by Streptoalloteichus sp. 1454-19*. J Antibiot 1999, 52(9): 775.

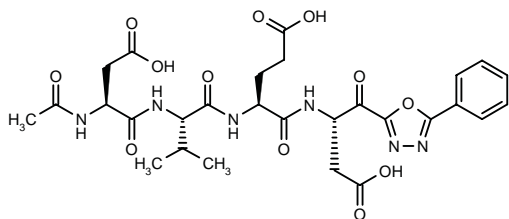
CQ-0010**282321**

2-(Acetyl-L-tyrosyl-L-valyl-L-alanyl-L-aspartyl)-5-phenyl-1,3,4-oxadiazole



C31 H36 N6 O9; Mol wt: 636.6584

ACTION – Cysteine protease inhibitor with relatively low molecular weight, high potency, reversible inhibition and selectivity with respect to various cysteine proteases. It inhibits caspases such as caspase 8 (FLICE or Mch5), caspase 1 (IL-1 β -converting enzyme or ICE) and caspase 3 (YAMA or CPP32), with respective IC₅₀ values of 0.02, 0.3 and 3.3 μ M. CQ-0010 was an extremely potent and selective inhibitor of IL-1 β production, with an IC₅₀ value of 0.3-0.5 μ M in THP-1 cells and human whole blood, while having no effect against TNF- α production. Potentially useful in the treatment of inflammation, diabetes, septic shock, rheumatoid arthritis and Alzheimer's disease, among others. Another compound from this series of cysteine protease inhibitors is:



CQ-0011 [282322]: C28 H34 N6 O12

SOURCE – Cortech.

REFERENCES

1. Spruce, L.W. et al. (Cortech, Inc.) *Cysteine protease inhibitors*. US 6004933, WO 9954317.

ISIS-18669**283041**

Phosphorothioate oligodeoxynucleotide whose sequence is: 5'-GCAGGGCTCGCAGATGGT-3'

ACTION – Antisense phosphorothioate oligodeoxynucleotide that specifically hybridizes with nucleic acids encoding human CD40 and modulates its expression. It was shown to inhibit CD40 mRNA levels by 34% at a concentration of 150 nM. Potentially useful for the treatment of immune-associated, inflammatory or hyperproliferative disorders, i.e., graft-versus-host disease, allograft rejection, autoimmune diseases, asthma, rheumatoid arthritis, inflammatory bowel disease, psoriasis and cancer. Other exemplified oligonucleotides are:

Phosphorothioate oligodeoxynucleotide whose sequence is: 5'-CCAGGCGGCAGGACCACT-3'

283042

Phosphorothioate oligodeoxynucleotide whose sequence is: 5'-GACCAGGCGGCAGGACCA-3'

283043

Phosphorothioate oligodeoxynucleotide whose sequence is: 5'-GGTCAGCAAGCAGCCCCA-3'

283044

Phosphorothioate oligodeoxynucleotide whose sequence is: 5'-AACTGCCTGTTTGCCAC-3'

283045

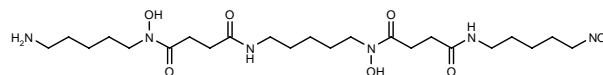
SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Bennett, C.F. and Cowser, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of CD40 expression*. WO 9957320.

IMMUNOMODULATING AGENTS**IC-202B****281037**

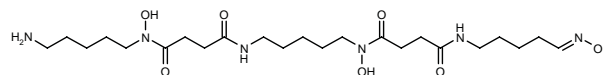
*N*¹-(5-Aminopentyl)-*N*¹-hydroxy-*N*⁴-[5-[*N*-hydroxy-3-[*N*-(5-nitropentyl)carbamoyl]propionamido]pentyl]succinamide



C23 H44 N6 O8; Mol wt: 532.6346

M.p. 117-9 °C.

ACTION – Immunosuppressant isolated from the culture filtrate of *Streptoalloteichus* sp. 1454-19, whose immunosuppressive activity was determined in a mixed lymphocyte culture reaction (IC₅₀ = 1.6 μ g/ml) and against mitogen-induced lymphocyte blastogenesis (IC₅₀ = 2.5 and 4.4 μ g/ml, respectively, against concanavalin A and lipopolysaccharide). Another compound isolated from this source is:



IC-202C [281038]: C23 H44 N6 O7

SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

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SIROLIMUS

Rec INN; BAN; USAN

175652

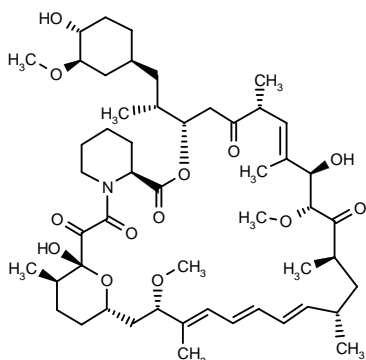
[1*R*,9*S*,12*S*[1'*R*(1''*S*,3''*R*,4''*R*)],15*R*,18*R*,19*R*,21*R*,23*S*,30*S*,32*S*,35*R*]-1,18-Dihydroxy-12-[2-(4-hydroxy-3-methoxy-1-cyclohexyl)-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-azatri-cyclo[30.3.1.0^{4,9}]hexatriaconta-16(*E*),24(*E*),26(*E*),28(*E*)-tetraen-2,3,10,14,20-pentaone

(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34*aS*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34*a*-Hexadecahydro-9,27-dihydroxy-3-[2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1(*R*)-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4]-oxaazacyclohentacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentaone

AY-22989

Rapamycin⁺

Wy-090217



C51 H79 N O13; Mol wt: 914.1791

ACTION – Immunosuppressant.

INDICATION – Prophylaxis of organ rejection in patients receiving renal transplants. It is recommended that sirolimus be used in a regimen with ciclosporin and corticosteroids.

PRESENTATION – Oral solution in glass bottles or unit-of-use pouches, 1 mg/ml.

PROPRIETARY NAME – Rapamune (US).**SOURCE** – Wyeth-Ayerst.

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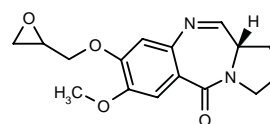
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ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

281384

(11a*S*)-7-Methoxy-8-(oxiranylmethoxy)-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one



C16 H18 N2 O4; Mol wt: 302.3282

ACTION – Antineoplastic agent, a bifunctional pyrrolo-[2,1-*c*][1,4]benzodiazepine (PBD) compound shown to induce sequence-specific interstrand DNA crosslinks at low micromolar concentrations, resulting in superior DNA binding affinity compared to the parent compound DC-81. It had significant cytotoxicity against the human ovarian carcinoma cell lines SKOV-3, A2780 and CH1 (IC₅₀ = 1.3, 0.045 and 0.059 μM, respectively), as well as against cisplatin-resistant variants of the CH1 and A2780 lines (IC₅₀ = 0.047 and 0.2 μM, respectively).

SOURCE – Institute of Cancer Research, London (GB).

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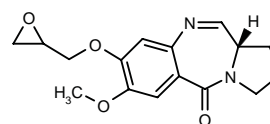
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ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

281384

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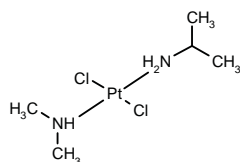
SOURCE – Institute of Cancer Research, London (GB).

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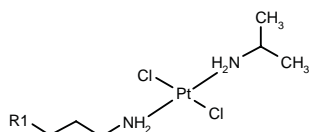
281392

trans-[(Diisopropylamine)(isopropylamine)(dichloro)]-platinum(II)



C₃ H₉ N . C₂ H₇ N . Cl₂ Pt; Mol wt: 370.1814

ACTION – Antineoplastic agent, a *trans*-platinum complex with higher cytotoxicity than cisplatin in several human tumor cell lines sensitive to cisplatin including Jurkat acute leukemia, cervical epithelial HeLa and Vero cells (IC₅₀ = 5, 32 and 47 μM, respectively, vs. 7, 38 and 50 μM, respectively, for cisplatin), as well as in tumor cell lines overexpressing *ras* oncogenes and resistant to cisplatin such as promyelocytic leukemia HL-60 and *ras*-transformed murine keratinocyte Pam 212-*ras* cells (IC₅₀ = 17 and 6 μM, respectively, vs. 25 and 156 μM, respectively, for cisplatin); it induced apoptosis in the Pam 212-*ras* cells. In laboratory studies, the compound was shown to induce higher amounts of DNA interstrand crosslinks than cisplatin and is able to bind to alternating purine–pyrimidine sequences. Other *trans*-platinum complexes are:



Compound	R1	Formula
281393	H	C ₆ H ₁₈ Cl ₂ N ₂ Pt
281394	Me	C ₇ H ₂₀ Cl ₂ N ₂ Pt

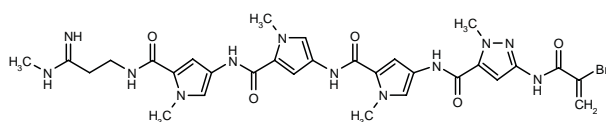
SOURCES – Universidad Autónoma de Madrid, Madrid (ES); CSIC, Madrid (ES).

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281606

3-(2-Bromo-2-propenamido)-1-methyl-*N*-[1-methyl-5-[*N*-[1-methyl-5-[*N*-[1-methyl-5-[*N*-[2-(*N*¹-methylamidino)-ethyl]carbamoyl]pyrrol-3-yl]carbamoyl]pyrrol-3-yl]carbamoyl]pyrrol-3-yl]-1 *H*-pyrazole-5-carboxamide



C₃₀ H₃₅ Br N₁₂ O₅; Mol wt: 723.5895

ACTION – Antineoplastic alkylating agent, a representative compound from a series of acryloyl distamycin derivatives with potential in the treatment of mammary, lung, bladder and colon carcinomas, ovarian and endometrial tumors, as well as soft tissue and bone sarcomas and hematological malignancies such as leukemia.

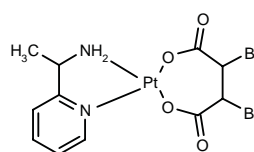
SOURCE – Pharmacia & Upjohn (Pharmacia).

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- Cozzi, P. et al. (Pharmacia & Upjohn SpA) *Acryloyl derivs. analogous to distamycin, process for preparing them, and their use as antitumor agents.* WO 9950265.

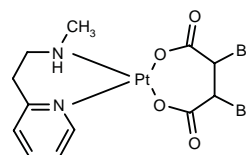
282036

[[1-(2-Pyridinyl)ethylamine](2,3-dibromosuccinato)]-platinum(II)



C₇ H₁₀ N₂ . C₄ H₂ Br₂ O₄ Pt; Mol wt: 591.1138

ACTION – Carcinostatic agent with human telomerase-inhibitory activity (IC₅₀ = 0.8 μM). Compound inhibited the proliferation of human cervical cancer-derived HeLa-S3 cells and WI-38 cells derived from normal lung tissue with IC₅₀ values of 80 and 30 μM, respectively; its effect against HeLa-S3 cells was shown to be time-dependent. Another platinum(II)-containing compound is:



282037: C₈ H₁₂ N₂ . C₄ H₂ Br₂ O₄ Pt

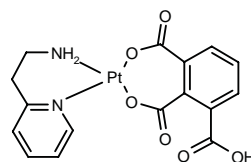
SOURCE – Chugai.

REFERENCES

- Kato, N. et al. (Chugai Pharmaceutical Co. Ltd.) *Telomerase inhibitors.* WO 9941262.

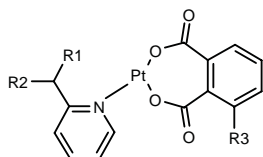
282038

[[2-(Pyridin-2-yl)ethanamine](3-carboxyphthaladioato)]-platinum(II)



C₉ H₄ O₆ Pt . C₇ H₁₀ N₂; Mol wt: 525.3746

ACTION – Carcinostatic agent with human telomerase-inhibitory activity (IC₅₀ = 1.2 μM). Other platinum(II)-containing compounds include the following:



Compound	R1	R2	R3	Formula
282039	NH ₂	H	CO ₂ H	C ₁₅ H ₁₂ N ₂ O ₆ Pt
282040	NH ₂	Me	H	C ₁₅ H ₁₄ N ₂ O ₄ Pt
282041	NH ₂	Me	CO ₂ H	C ₁₆ H ₁₄ N ₂ O ₆ Pt
282042	CH ₂ NHMe	H	CO ₂ H	C ₁₇ H ₁₆ N ₂ O ₆ Pt

SOURCE – Chugai.

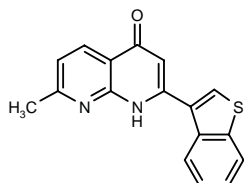
REFERENCES

1. Kato, N. et al. (Chugai Pharmaceutical Co. Ltd.) *Telomerase inhibitors*. WO 9941261.

ANTIMITOTIC DRUGS

281387

2-(1-Benzothien-3-yl)-7-methyl-1,8-naphthyridin-4(1H)-one



C₁₇H₁₂N₂O S; Mol wt: 292.3608

M.p. 264 °C.

ACTION – Antineoplastic agent, an inhibitor of tubulin polymerization ($IC_{50} = 0.37 \mu M$), with comparable activity to other antimitotic agents such as podophyllotoxin, combretastain A-4 and NSC-664171 ($IC_{50} = 0.59, 0.66$ and $0.49 \mu M$, respectively). Compound also strongly inhibited the binding of radiolabeled colchicine to tubulin (65% inhibition at $5 \mu M$) and was active in the nanomolar range against several human tumor cell lines including leukemia HL-60, non-small cell lung NCI-H23, colon SW-620, CNS U251, melanoma SK-MEL-5, ovarian OVCAR-3, renal RXF-393, prostate PC-3, and breast MDA-MB-435 and MDA-N cancer cell lines.

SOURCE – National Institutes of Health, Bethesda, MD (US).

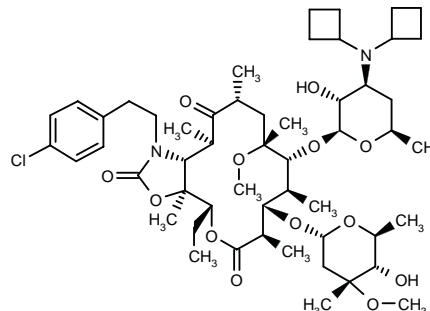
REFERENCES

1. Zhang, S.-X. et al. *Antitumor agents*. 196. *Substituted 2-thienyl-1,8-naphthyridin-4-ones: Their synthesis, cytotoxicity, and inhibition of tubulin polymerization*. J Med Chem 1999, 42(20): 4081.

HORMONAL AGENTS

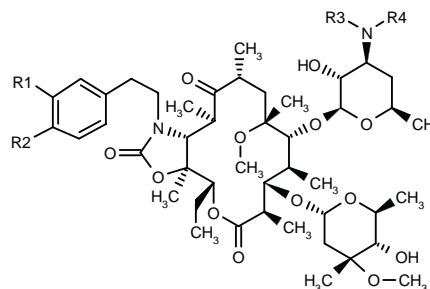
281598

3',3'-N-Bis(cyclobutyl)-11-[2-(4-chlorophenyl)ethylamino]-11-deoxy-3',3'-N-bis(desmethyl)-6-O-methylerythromycin A 11-N,12-O-(cyclic carbamate)



C₅₃H₈₃ClN₂O₁₃; Mol wt: 991.6927

ACTION – A potent antagonist of luteinizing hormone-releasing hormone (LHRH), potentially useful in the treatment of disorders mediated by sex hormones including prostate cancer, endometriosis, uterine fibrosis and precocious puberty. Activity was evaluated *in vitro* in a binding assay ($pK_i = 8.62$ for the rat pituitary LHRH receptor) and in a functional assay by measuring the concentration of test compound required to shift the response curve for the agonist leuprolide to a 2-fold higher concentration in rat pituitary cells ($pA_2 = 9.90$). A compound within a series of 3',3'-N-bis-substituted macrolides, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
281599	Cl	Cl	cyclobutyl	cyclobutyl	C ₅₃ H ₈₂ Cl ₂ N ₂ O ₁₃
281600	H	Cl	i-Pr	cyclobutyl	C ₅₂ H ₈₃ ClN ₂ O ₁₃
281601	F	Cl	cyclopropyl-CH ₂	cyclopropyl-CH ₂	C ₅₃ H ₈₂ ClF ₂ N ₂ O ₁₃
281602	Cl	F	cyclobutyl	cyclobutyl	C ₅₃ H ₈₂ ClF ₂ N ₂ O ₁₃
281603	F	F	cyclopropyl-CH ₂	cyclopropyl-CH ₂	C ₅₃ H ₈₂ F ₂ N ₂ O ₁₃
281605	F	F	cyclobutyl	cyclobutyl	C ₅₃ H ₈₂ F ₂ N ₂ O ₁₃

SOURCE – Abbott.

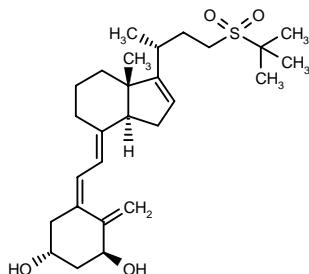
REFERENCES

1. Sauer, D.R. et al. (Abbott Laboratories Inc.) *3',3'-N-Bis-substd. macrolide LHRH antagonists*. US 5972898, WO 9950276.

JK-1624SO2

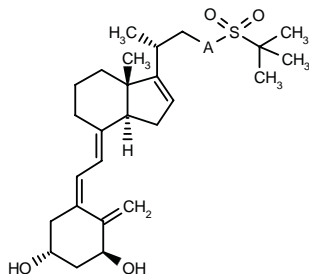
280313

23-(*tert*-Butylsulfonyl)-16,17-dehydro-1 α -hydroxy-24,25,26,27-tetranorvitamin D₃



C27 H42 O4 S; Mol wt: 462.6908

ACTION – Vitamin D₃ (calcitriol) analogue with potent transcriptional activity in rat osteosarcoma ROS 17/2.8 cells, being only 2-fold less active than the parent compound (ED₅₀ = 0.8 and 0.35 nM, respectively). In murine malignant melanoma B16 cells, it was at least as active in inhibiting proliferation as calcitriol; in contrast to the latter, it produced no increase in urinary calcium excretion in rats after 1 week of repeated oral treatment (10 μ g/kg). Within this class of sulfone analogues of vitamin D₃, the following are also described:



Compound	A	Formula
QW-1624F2-25SO2-1 [280314]	-CH2C(F)2-	C ₂₈ H ₄₂ F ₂ O ₄ S
QW-1623E-diene-24F-25SO2-1 [280315]	-CH=C(F)-	C ₂₈ H ₄₁ FO ₄ S

SOURCES – Johns Hopkins University, Baltimore, MD (US); M.D. Anderson Cancer Center, Houston, TX (US).

REFERENCES

1. Posner, G.H. et al. *Conceptually new sulfone analogues of the hormone 1 α ,25-dihydroxyvitamin D₃: Synthesis and preliminary biological evaluation.* J Med Chem 1999, 42(18): 3425.

CANCER IMMUNOTHERAPY

282323

L-Alanyl-L-alanyl-L-aspartyl-L-histidyl-L-arginyl-L-glutamyl-L-leucyl-L-glutamyl-L-leucyl-L-seryl-L-iso-leucyl-L-seryl-L-seryl-L-cysteinyl-L-leucyl-L-glutamyl-L-glutamyl-L-leucine

C84 H143 N27 O28 S; Mol wt: 2011.2810

ACTION – Polypeptide that binds to MHC class I and class II molecules and contains the HLA-A2-binding sequence of the tumor antigen NY-ESO-1. Compound stimulates the recognition and proliferation of CD4+ cells specific for complexes of the peptide and HLA-DR53. Potentially useful for the treatment, prevention, diagnosis and screening of cancer. Other related polypeptides are:

L-Valyl-L-leucyl-L-leucyl-L-lysyl-L-glutamyl-L-phenylalanyl-L-threonyl-L-valyl-L-seryl-glycyl-L-asparagyl-L-iso-leucyl-L-leucyl-L-threonyl-L-iso-leucyl-L-arginyl-L-leucyl-L-threonine

282327

L-Prolyl-L-leucyl-L-prolyl-L-valyl-L-prolyl-glycyl-L-valyl-L-leucyl-L-leucyl-L-lysyl-L-glutamyl-L-phenylalanyl-L-threonyl-L-valyl-glycyl-L-asparagyl-L-iso-leucine

282331

SOURCE – Ludwig Institute for Cancer Research, New York, NY (US).

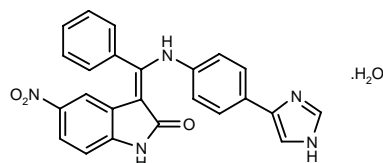
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1. Stockert, E. et al. (Ludwig Institute for Cancer Research) *Isolated peptides corresponding to amino acid sequences of NY-ESO-1, wherein bind to MHC class I and MHC class II molecules, and uses thereof.* WO 9953938.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

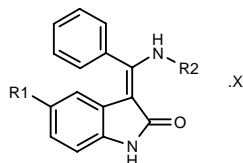
281865

3-[(*Z*)-1-[4-(1*H*-Imidazol-4-yl)phenylamino]-1-phenyl-methylene]-5-nitro-2,3-dihydro-1*H*-indol-2-one hydrate



C24 H17 N5 O3 . H2O; Mol wt: 441.4451

ACTION – Antiproliferative agent, an inhibitor of cyclin-dependent kinases (CDKs) shown to inhibit cyclin D1/CDK4 activity ($IC_{50} = 1.0 \mu M$) and the proliferation of human leiomyosarcoma SK-UT-1B cells ($IC_{50} = 0.34 \mu M$) *in vitro*. *In vivo*, it produced a 65% reduction in tumor weight in nude mice bearing non-small cell lung NCI-H460 tumors when given at 100 mg/kg/day p.o. x 2 weeks. Other compounds from this series of substituted indolinones include the following:



Compound	R1	R2	X	Formula
281866	NO2	1,2,3,4-tetrahydro-6-isoquinolinyl	HCl H2O	$C_{24}H_{20}N_4O_3$.HCl.H ₂ O
281867	NO2	2-Ac-1,2,3,4-tetrahydro-6-isoquinolinyl		$C_{26}H_{21}N_3O_4$
281868	NO2	4-(1-pyrrolidinyl-CH2CH2)-Ph	H2O	$C_{27}H_{26}N_4O_3 \cdot H_2O$
281869	NO2	4-(1-Me-2-imidazolyl)-Ph	H2O	$C_{25}H_{19}N_5O_3 \cdot H_2O$
281870	NO2	4-(1-pyrrolidinyl-CH2)-Ph	H2O	$C_{26}H_{24}N_4O_3 \cdot H_2O$
281871	H	4-(imidazo[1,2-a]pyrimidin-2-yl)-Ph	H2O	$C_{27}H_{19}N_5O \cdot H_2O$
281874	NO2	4-(2,5-dioxo-1-pyrrolidinyl-CH2)-Ph		$C_{26}H_{20}N_4O_5$

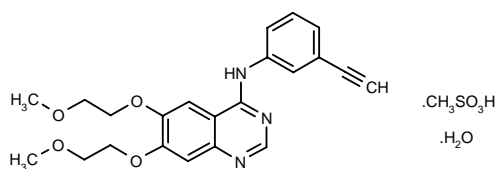
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Grell, W. et al. (Boehringer Ingelheim Pharma KG) *Subst. indolinones as kinase inhibitors*. DE 19815020, WO 9951590.

282450

N-[6,7-Bis(2-methoxyethoxy)quinazolin-4-yl]-*N*-(3-ethynylphenyl)amine methanesulfonate hydrate



C22 H23 N3 O4 . C H4 O3 S . H2O; Mol wt: 507.5611

ACTION – Hydrate form of the mesylate salt of a known antiproliferative compound and tyrosine kinase inhibitor, found to possess certain advantages over the hydrochloride form –CP-358774, currently in phase II trials– such as greater water solubility. Potentially useful for the treatment of hyperproliferative disorders such as cancer.

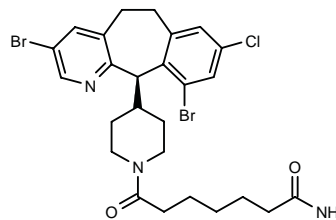
SOURCE – Pfizer.

REFERENCES

1. Allen, D.J.M. et al. (Pfizer Products Inc.) *N*-(3-Ethynylphenylamino)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine mesylate anhydrate and monohydrate. WO 9955683.

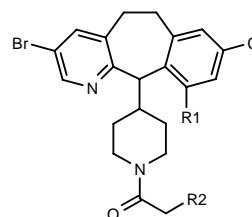
283499

(+)-7-[4-[3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl]piperidin-1-yl]-7-oxoheptanamide



C26 H30 Br2 Cl N3 O2; Mol wt: 611.8030

ACTION – Antineoplastic agent with inhibitory activity against protein farnesyltransferase. It showed *in vitro* enzyme inhibition ($IC_{50} = 0.0033 \mu M$) and cellular activity, i.e., inhibition of Ras processing in COS cells ($IC_{50} = 0.015 \mu M$). Potentially useful in the treatment of pancreatic, breast, prostate, lung, thyroid follicular, myelodysplastic, epidermal carcinoma, bladder carcinoma and colon tumors and myeloid leukemia. Other exemplified tricyclic compounds include the following:



Compound	R1	R2	Isomer	Formula
283501	Br	CH2CH2N(Me)2		$C_{25}H_{30}Br_2ClN_3O$
283502	Cl	CH2CH2N(Me)2		$C_{25}H_{30}BrCl_2N_3O$
283503	Cl	2-oxo-1-pyrrolidinyl		$C_{25}H_{26}BrCl_2N_3O_2$
283504	Cl	CH2CON(Me)2		$C_{25}H_{26}BrCl_2N_3O_2$
283505	Cl	1-pyrrolidinyl-COCH2		$C_{27}H_{30}BrCl_2N_3O_2$
283506	Cl	3-Pyr-CONHCH2CH2		$C_{29}H_{28}BrCl_2N_4O_2$
283507	Br	(CH2)4CO2Na	(+)-R	$C_{26}H_{28}Br_2ClN_2NaO_3$

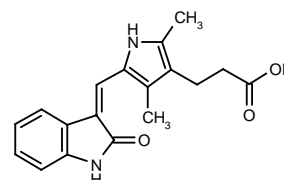
SOURCE – Schering-Plough.

REFERENCES

1. Njoroge, F.G. et al. (Schering Corp.) *Tricyclic antitumor farnesyl protein transferase inhibitors*. US 5994364.

283644

(*Z*)-3-[2,4-Dimethyl-5-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidenemethyl)-1*H*-pyrrol-3-yl]propionic acid



C18 H18 N2 O3; Mol wt: 310.3512

ACTION – Protein kinase activity modulator that inhibits receptor and nonreceptor tyrosine kinases and/or serine/threonine protein kinases, especially potent in inhibiting FLK-1 receptor and platelet-derived growth factor (PDGF) receptor tyrosine kinase activity and vascular endothelial growth factor (VEGF) activity in human umbilical vein endothelial cells (HUVEC), giving respective IC₅₀ values of 0.13, <1.2 and 0.42 μM. Compound also potently inhibited the growth of C6 glioma xenografts in athymic mice following oral administration (80-85% inhibition at a dose of 200 mg/kg/day p.o.). Potentially useful in the treatment and prevention of cancer, diabetes, hepatic cirrhosis, cardiovascular disorders such as atherosclerosis, angiogenesis, autoimmune diseases and renal diseases.

SOURCE – Sugan (Pharmacia).

REFERENCES

1. Tang, P.C. et al. (Sugen, Inc.) *Pyrrole subst. 2-indolinone protein kinase inhibitors*. WO 9961422.

HYB-165

280900

Chimeric DNA/RNA mixed-backbone oligonucleotide whose sequence is: 5'-GCGUGCCTCCTCACUGGC-3', in which the first and last four nucleosides flanking 5'- and 3'-ends are 2'-O-methylribonucleosides and the central ten nucleosides are deoxynucleosides containing phosphorothioate internucleotide linkages

ACTION – Antineoplastic agent, a chimeric DNA/RNA mixed-backbone antisense oligonucleotide targeting protein kinase A (PKA) with cytotoxic activity against human breast cancer ZR-75-1 cells and synergistic inhibitory effect on ZR-75-1 colony formation when used in combination with docetaxel. Compound administered orally to nude mice bearing human cancer xenografts, alone and in combination with various cytotoxic agents such as taxanes and platinum derivatives, demonstrated a dose-dependent inhibition of tumor growth, growth factor production and angiogenesis, inducing a significant increase in survival; a synergistic effect was observed with combinations. Histochemical analysis showed that the antitumor effect of compound was accompanied by inhibition of the expression of different factors of the epidermal growth factor (EGF) family, inhibition of angiogenesis and an increase in p27 expression. Synergistic antitumor activity has also been observed in combination with ionizing radiation in human colon and ovarian cancer cell lines. Compound recently completed a phase I trial in cancer patients by the i.v. route and demonstrated an excellent toxicity profile.

SOURCE – Hybridon.

REFERENCES

1. Agrawal, S. (Hybridon, Inc.) *Modified protein kinase A-specific oligonucleotides and methods of their use*. WO 9840479.
2. Bianco, C. et al. *Synergistic antiproliferative effects of ionizing radiations with anti-epidermal growth factor receptor monoclonal antibody C225 and protein kinase A antisense oligonucleotide HYB 165*. Int J Radiat Oncol Biol Phys 1999, 45(3, Suppl. 1): Abst 28.
3. Tortora, G. et al. *Cooperative inhibitory effect of novel mixed backbone oligonucleotide targeting protein kinase A in combination with docetaxel and anti-epidermal growth factor-receptor antibody on human breast cancer cell growth*. Clin Cancer Res 1999, 5(5): 875.

4. Tortora, G. et al. *Oral administration of chimeric MBO antisense-protein kinase A inhibits growth, angiogenesis and growth factor production and cooperates with cytotoxic drugs in human cancer xenografts*. Eur J Cancer 1999, 35(Suppl. 4): Abst 1436.

5. Zhang, R. et al. *Novel mixed-backbone oligonucleotides (MBO) targeted at protein kinase A with improved in vivo antitumor activities against cancer xenografts*. Proc Amer Assoc Cancer Res 1997, 38: Abst 2118.

ISIS-12884

281352

Phosphorothioate oligonucleotide whose sequence is: 5'-GTCCCCACCGCCACTCCTGG-3', in which the G, T, T, T, G and G residues in positions 1, 2, 15, 18, 19 and 20 are 2'-fluoro-substituted and the C residues in positions 3, 4, 5, 6, 16 and 17 are 2'-fluoro-5-methylcytosines

ACTION – Phosphorothioate antisense oligonucleotide targeted to nucleic acids encoding human HER-2 (also known as c-neu, ErbB-2 and HER-2/neu), potentially useful in the treatment of hyperproliferative disorders, particularly cancers associated with overexpression of HER-2 such as breast, ovarian and gastric cancer. Compound inhibited human HER-2 mRNA levels in human ovarian carcinoma SKOV-3 cells by 96% at a concentration of 300 nM, and it reduced human HER-2 protein levels in these cells by 72% at this concentration. It also inhibited SKOV-3 cell proliferation by 61% at 300 nM. In addition, it was shown to inhibit human epidermal growth factor (EGF) receptor mRNA expression by 90% in SKOV-3 cells. Other exemplified antisense oligonucleotides include the following:

Phosphorothioate 2'-deoxyoligonucleotide whose sequence is: 5'-GGTCAGGCAGGCTGTCCGGC-3'

281353

Phosphorothioate 2'-deoxyoligonucleotide whose sequence is: 5'-GTCCCCACCGCCACTCCTGG-3'

281354

Phosphorothioate 2'-deoxyoligonucleotide whose sequence is: 5'-GCATGGCAGGTTCCCCTGGA-3'

281355

Phosphorothioate 2'-deoxyoligonucleotide whose sequence is: 5'-GTCCCCACCGCCACTCCTGG-3', in which all the C residues are 5-methylcytosines

281356

Phosphorothioate oligonucleotide whose sequence is: 5'-GTCCCCACCGCCACTCCTGG-3', in which the G, T, C, C, C, C, T, C, C, T, G and G residues in positions 1, 2, 3, 4, 5, 6, 15, 16, 17, 18, 19 and 20 are 2'-O-propyl-substituted

281357

SOURCES – Isis Pharmaceuticals; Penn State Research Foundation, University Park, PA (US).

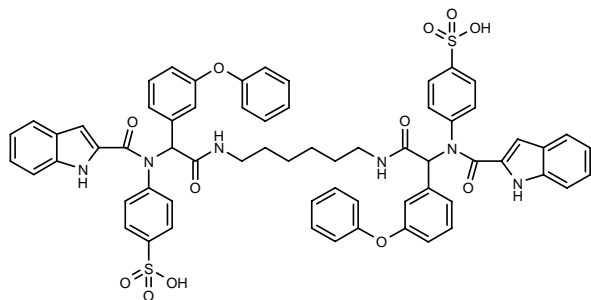
REFERENCES

1. Bennett, C.F. et al. (Isis Pharmaceuticals, Inc.; Penn State Research Foundation) *Antisense oligonucleotide modulation of human HER-2 expression*. WO 9948906.

ANGIOGENESIS INHIBITORS

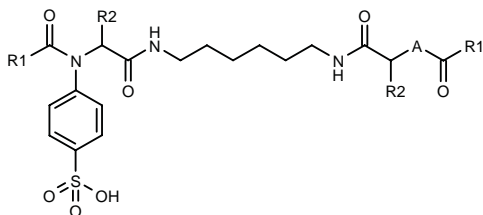
281512

N,N'-(Hexane-1,6-diyl)bis[2-[*N*-(1*H*-indol-2-ylcarbonyl)-*N*-(4-sulfophenyl)amino]-2-(3-phenoxyphenyl)acetamide]



C₆₄ H₅₆ N₆ O₁₂ S₂; Mol wt: 1165.3080

ACTION – Agent that inhibits the interaction of glycosaminoglycans with the proteins they activate, particularly growth factors, with potential in the treatment of cancers expressing erbB or epidermal growth factor (EGF) receptors such as adenocarcinoma, breast cancer, glial cell-derived ovarian cancer, prostate cancer, melanoma and other skin cancers, squamous cell carcinoma of the lung, gastric cancer, astrocytomas, oligodendrogliomas, malignant gliomas, schwannomas, type 1 or 2 neurofibromatosis and pituitary cancer. Compound inhibited heparin-neuregulin binding with an IC₅₀ value of 3 μM; it was also shown to inhibit heparin-bFGF (basic fibroblast growth factor) and heparin-VEGF (vascular endothelial growth factor) binding with IC₅₀ values of 0.2 and 0.3 μM. In addition, it inhibited recombinant human glial growth factor-2 (rhGGF2)-stimulated DNA synthesis in Schwann cells and human breast carcinoma MCF-7 cells at low micromolar concentrations. Compound also completely blocked the rhGGF2-stimulated responses of 32D.23 human hemopoietic cells transfected with erbB receptors at a concentration of 10 μM, and it potently inhibited the rhGGF2-stimulated responses of MCF-7 and human prostate LNCAP tumor cells. It was also found to concentration-dependently inhibit bFGF- or VEGF-stimulated proliferation of HUVEC (human umbilical vein endothelial cells) and exhibited antiangiogenic activity *in vivo* in a murine corneal implant model, where it produced a significant reduction in angiogenic activity induced by VEGF-impregnated pellets at 8-16 μmol/kg i.p. Other exemplified compounds include the following:



Compound	R1	R2	A	Formula
281513	1-Naph	3-(PhO)-Ph	-O-	C ₆₂ H ₅₃ N ₃ O ₁₀ S
281514	1-Naph	3-(PhO)-Ph	-N(4-SO ₃ H-Ph)-	C ₆₈ H ₅₈ N ₄ O ₁₂ S ₂
281515	2-indolyl	cyclohexyl	-O-	C ₄₆ H ₅₅ N ₃ O ₆ S

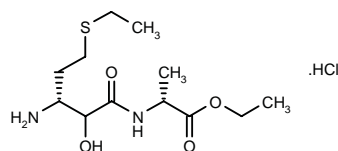
SOURCES – Cambridge NeuroScience; Repligen.

REFERENCES

- Herlihy, W.C. et al. (Repligen Corp.;Cambridge NeuroScience, Inc.) *Protein-carbohydrate binding antagonists*. WO 9950246.

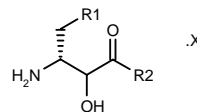
283148

N-[3(*R*)-Amino-5-(ethylsulfanyl)-2-hydroxypentanoyl]-D-alanine ethyl ester hydrochloride



C₁₂ H₂₄ N₂ O₄ S . HCl; Mol wt: 328.8585

ACTION – Potent inhibitor of methionine aminopeptidase type 2 (IC₅₀ = 0.09 μM) that is therefore expected to be useful for inhibiting angiogenesis and for the treatment of disease conditions involving angiogenesis such as diabetic retinopathy, tumor growth and inflammatory disorders. It is a reversible inhibitor of the enzyme and may therefore display improved pharmaceutical properties and reduced side effects compared to currently available irreversible inhibitors such as fumagillin and TNP-470. Other exemplified substituted β-amino acids are:



Compound	R1	R2	X	Formula
283149	CH ₂ SMe	OH		C ₆ H ₁₃ NO ₃ S
283150	CH ₂ SEt	NHC(Me)2CO ₂ Me	HCl	C ₁₃ H ₂₆ N ₂ O ₄ S.HCl
283151	CH ₂ SEt	-L-Ser-OEt	HCl	C ₁₂ H ₂₄ N ₂ O ₅ S.HCl
283152	cyclohexyl	2,6-(Cl)2-Ph-CH ₂ CH ₂ NH	HCl	C ₁₈ H ₂₆ Cl ₂ N ₂ O ₂ .HCl

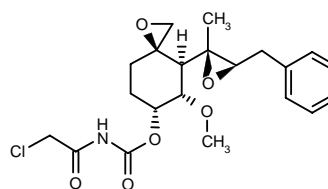
SOURCE – Abbott.

REFERENCES

- Craig, R.A. et al. (Abbott Laboratories Inc.) *Subst. β-amino acid inhibitors of methionine aminopeptidase-2*. WO 9957098.

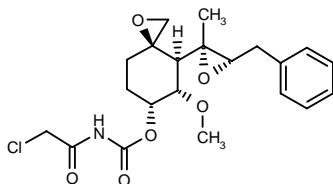
283667

(±)-*N*-(2-Chloroacetyl)carbamic acid (3*RS*,4*SR*,5*SR*,6*RS*)-4-[3(*RS*)-benzyl-2(*RS*)-methyloxiranyl]-5-methoxy-1-oxaspiro[2.5]oct-6-yl ester



C₂₁ H₂₆ Cl N O₆; Mol wt: 423.8904

ACTION – Angiogenesis inhibitor giving an IC_{50} value of $0.043 \mu M$ for inhibition of human umbilical vein endothelial cell (HUVEC) growth. Potentially useful for inhibiting tumor cell growth and/or tumor metastasis, as well as for the treatment of diabetic retinopathy and inflammatory disorders such as rheumatism and psoriasis. Another representative fumagillin analogue is:



283668: C21 H26 Cl N O6

SOURCE – BioChem Pharma.

REFERENCES

1. Lamothe, S. et al. (BioChem Pharma Inc.) *Fumagillin analogs and their use as angiogenesis inhibitors*. WO 9961432.

Tip-19.40

281371

N-Acetyl-L-lysyl-L-aspartyl-L-phenylalanyl-L-threonyl-L-alanyl-L-tyrosyl-L-arginyl-L-tryptophyl-L-arginyl-L-leucyl-L-seryl-L-histidyl-L-arginyl-L-prolyl-L-lysyl-L-aspartyl-L-leucyl-L-tyrosyl-L-seryl-L-isoleucyl-L-valyl-L-arginyl-L-arginyl-L-alanyl-L-aspartyl-L-arginine

C150 H235 N49 O39; Mol wt: 3348.8110

ACTION – Peptide with antiangiogenic and antineoplastic activity, a hybrid of subsequences of the angiogenic homology regions (AHR) of thrombospondin-1 and endostatin. *In vitro*, compound was shown to concentration-dependently inhibit the proliferation of bovine aortic endothelial cells, and *in vivo*, it was shown to markedly inhibit tumor growth in mice bearing melanoma B16 at 20-30 mg/kg/day s.c. x 2 weeks.

SOURCES – Children's Medical Center, Cambridge, MA (US); Yissum.

REFERENCES

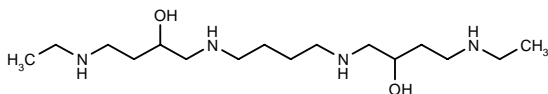
1. Ben-Sasson, S.A. (Children's Medical Center Corp.; Yissum Research Development Co.) *Endostatin derived peptides with anti-angiogenic and anti-cancer activity*. WO 9948924.

OTHER ONCOLYTIC DRUGS

281300

3,8,13,18-Tetrazaicosane-6,15-diol

1,1'-(Butane-1,4-diyl)bis(imino)bis[4-(ethylamino)-2-butanol]



C16 H38 N4 O2; Mol wt: 318.5022

ACTION – Antineoplastic and antidiarrheal agent, a representative compound from a series of hydroxylated analogues of therapeutically active polyamines such as diethylhomospermine (DEHSPM) that are metabolized to products rapidly and easily cleared from tissues and are thus expected to be less toxic than parent compounds. Compared to DEHSPM, compound displayed similar growth-inhibitory activity against murine leukemia L1210 cells ($IC_{50} = 0.6$ and $0.07 \mu M$ vs. 0.2 and $0.07 \mu M$ for DEHSPM, at 48 and 96 h, respectively), similar activity in competing with [3H]-spermidine for uptake into L1210 cells ($K_i = 1.8 \mu M$ vs. $1.4 \mu M$) and comparable antidiarrheal activity in the castor oil-induced diarrhea model in rats when given at 5 mg/kg s.c.; it showed at least 3-fold lower chronic toxicity in mice.

SOURCE – University of Florida, Gainesville, FL (US).

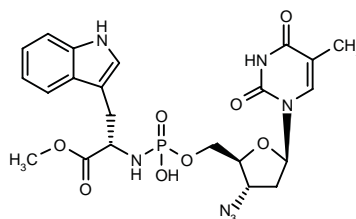
REFERENCES

1. Bergeron, R.J. Jr. (University of Florida) *Hydroxy polyamines*. US 5962533.

281520

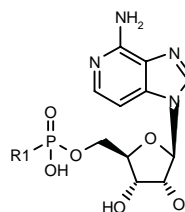
3'-Azido-3'-deoxy-5'-O-[hydroxy(1-O-methyl-L-tryptophano)phosphoryl]thymidine

N-[(3'-Azido-3'-deoxythymidin-5'-O-yl)(hydroxy)-phosphoryl]-L-tryptophan methyl ester

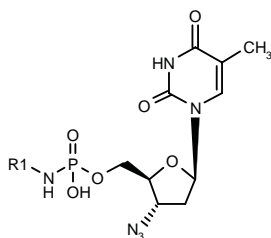


C22 H26 N7 O8 P; Mol wt: 547.4624

ACTION – Antiviral and antineoplastic nucleoside, a phosphoramidate derivative of zidovudine (AZT) reported to be considerably less toxic to leukemia and peripheral blood mononuclear cells than AZT while having only 3-fold lower cytotoxicity against breast cancer MCF-7 cells ($CC_{50} = 30$ nM vs. 10 nM for AZT). When administered i.p. to rats with methylnitrosourea-induced mammary carcinomas, compound was able not only to reduce the rate of tumor growth but to cause complete tumor regression in 10 days, whereas AZT only produced an 80% reduction of tumor growth. Significant anti-HIV-1 activity was also detected in peripheral blood mononuclear cells ($IC_{50} = 0.300-0.350 \mu M$). Compound is reported to be more soluble in water than AZT. Other compounds from this series of nucleoside derivatives include the following:



Compound	R1	Formula
281521	-L-Phe-OMe	$C_{21}H_{26}N_6O_8P$
281522	-L-Trp-OMe	$C_{23}H_{27}N_6O_8P$



Compound	R1	Formula
281523	-L-Phe-OMe	C ₂₀ H ₂₅ N ₆ O ₈ P
281524	-D-Phe-OMe	C ₂₀ H ₂₅ N ₆ O ₈ P
281525	-L-Trp-NHMe	C ₂₂ H ₂₇ N ₈ O ₈ P

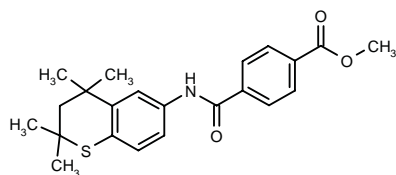
SOURCE – University of Minnesota, Minneapolis, MN (US).

REFERENCES

1. Wagner, C.R. and Griesgraber, G.W. (University of Minnesota) *Nucleosides with antiviral and anticancer activity*. WO 9949873.

281755^{1,3}

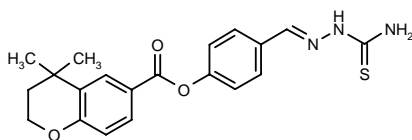
4-[N-(2,2,4,4-Tetramethyl-3,4-dihydro-2H-1-benzothio-pyran-6-yl)carbamoyl]benzoic acid methyl ester



C₂₂ H₂₅ N O₃ S; Mol wt: 383.5095

M.p. 162-4 °C.

ACTION – Antineoplastic agent, a heteroarotinoid that activates both retinoic acid receptor (RAR) and retinoid X receptor (RXR) subtypes (IC₅₀ = 225, 1004 and 152 nM, respectively, for RAR α , RAR β and RAR γ receptors; IC₅₀ = 84, 68 and 302 nM, respectively, for RXR α , RXR β and RXR γ receptors); it inhibited the growth of the squamous cell head and neck carcinoma (HNSCC) cell lines SCC-2 and SCC-38 (64 and 37% inhibition, respectively, at 10 μ M). In nude mice bearing SCC-38 xenografts, compound (10 mg/kg/day p.o. 5 days/week for 4 weeks) induced a significant reduction in tumor size, with complete tumor regression in 4 of 5 mice treated. It was able to inhibit AP-1-driven transcription in CV-1 cells. Another heteroarotinoid is:



281754¹⁻³: C₂₀ H₂₁ N₃ O₃ S

SOURCES – University of Oklahoma Health Sciences Center, Oklahoma City, OK (US); Oklahoma State University, Stillwater, OK (US).

REFERENCES

1. Berlin, K.D. et al. (Oklahoma State University) *Heteroarotinoids - Anticancer agents with receptor specificity and TGase activity*. WO 9807716.
2. Benbrook, D.M. et al. *Biologically active heteroarotinoids exhibiting anticancer activity and decreased toxicity*. J Med Chem 1997, 40(22): 3567.
3. Zacheis, D. et al. *Heteroarotinoids inhibit head and neck cancer cell lines in vitro and in vivo through both RAR and RXR retinoic acid receptors*. J Med Chem 1999, 42(21): 4434.

281796

Human staufen polypeptide

Telomerase-associated protein 3

hStau
TEP3

ACTION – Human telomerase-associated protein that binds human telomerase RNA and may play a role in telomerase assembly, transport and regulation. Polynucleotides encoding this polypeptide, as well as antibodies having specific binding affinity for this polypeptide and methods of inhibiting telomerase, are also disclosed.

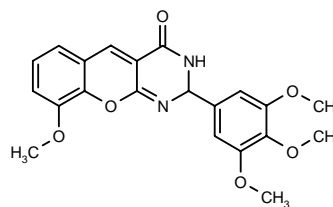
SOURCE – Johns Hopkins University, Baltimore, MD (US).

REFERENCES

1. Greider, C.W. and Le, S. (Johns Hopkins University) *Telomerase-associated proteins*. WO 9951255.

281875

9-Methoxy-2-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2H-[1]-benzopyrano[2,3-d]pyrimidin-4-one



C₂₁ H₂₀ N₂ O₆; Mol wt: 396.3970

Amorphous cream solid, m.p. 316 °C.

ACTION – Antineoplastic agent with selective activity against human ovarian cancer cell lines including A2780, Ovca5 and Ovca433 (IC₅₀ = 0.45, 5.52 and 2.85 μ M, respectively) and low cytotoxicity against nonovarian cancer cell lines such as lung carcinoma A549 and non-small cell lung carcinoma H460 (IC₅₀ > 10 μ M). Selected for further investigation.

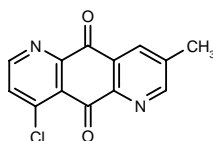
SOURCES – Cancer Research Campaign; De Montfort University, Leicester (GB).

REFERENCES

1. Hadfield, J.A. et al. *Synthesis and anticancer activities of 4-oxobenzopyrano[2,3-d]pyrimidines*. Anti-Cancer Drugs 1999, 10(6): 591.

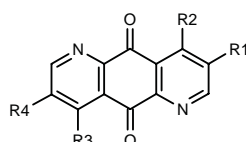
283508

9-Chloro-3-methylpyrido[2,3-*g*]quinoline-5,10-dione

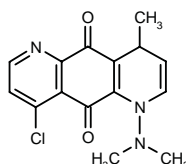


C₁₃H₇ClN₂O₂; Mol wt: 258.6633

ACTION – Antitumor anthraquinone that exhibits high cytotoxic activity against a range of tumor cell lines including murine leukemia P388, human lung carcinoma A549, human colon carcinoma HT-29 and human melanoma SK-MEL-28 cells (IC₅₀ = 0.15, 0.03, 0.04 and 0.03 mM, respectively). Other specifically claimed 1,5-diazaanthraquinones are:



Compound	R1	R2	R3	R4	Formula
283509	Et	H	H	Et	C ₁₆ H ₁₄ N ₂ O ₂
283510	Me	H	H	Me	C ₁₄ H ₁₀ N ₂ O ₂
283511	H	Me	Me	H	C ₁₄ H ₁₀ N ₂ O ₂
283512	Me	Et	Et	Me	C ₁₈ H ₁₈ N ₂ O ₂
283514	H	Me	Cl	H	C ₁₃ H ₇ ClN ₂ O ₂
283515	H	Cl	2-NO ₂ -Ph	H	C ₁₈ H ₈ ClN ₂ O ₄
283516	H	Me	N(Me) ₂	H	C ₁₅ H ₁₃ N ₃ O ₂



283513: C₁₅H₁₄ClN₃O₂

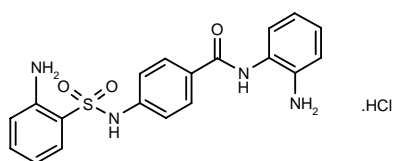
SOURCE – Universidad Complutense de Madrid, Madrid (ES).

REFERENCES

1. Avendano, C. et al. (Universidad Complutense de Madrid) *Antitumour 1,5-diazaanthraquinones*. WO 9959996.

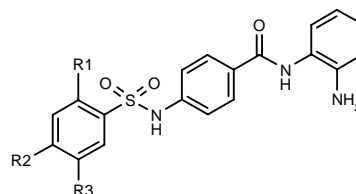
283692

N-(2-Aminophenyl)-4-(2-aminophenylsulfonamido)-benzamide hydrochloride



C₁₉H₁₈N₄O₃S · HCl; Mol wt: 418.9031

ACTION – Cell differentiation inducer, as shown using human ovarian cancer A2780 cells. Potentially useful for the treatment of tumors, autoimmune diseases, skin diseases and parasitic infections. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
283693	H	H	H	C ₁₉ H ₁₇ N ₃ O ₃ S
283694	Br	H	H	C ₁₉ H ₁₆ BrN ₃ O ₃ S
283695	H	NO ₂	H	C ₁₉ H ₁₆ N ₄ O ₅ S
283696	H	H	NH ₂	C ₁₉ H ₁₈ N ₄ O ₃ S
283697	H	NH ₂	H	C ₁₉ H ₁₈ N ₄ O ₃ S
283698	OMe	H	Br	C ₂₀ H ₁₈ BrN ₃ O ₄ S
283699	OMe	H	H	C ₂₀ H ₁₉ N ₃ O ₄ S

SOURCE – Mitsui Chemicals.

REFERENCES

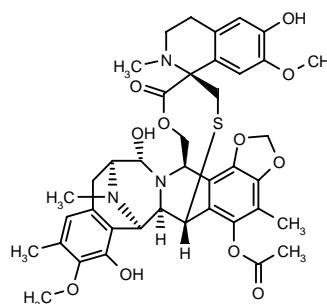
1. Tsuchiya, K. et al. (Mitsui Chemicals, Inc.) *Agents for inducing differentiation*. JP 99269140.

ECTEINASCIDIN 757

281757

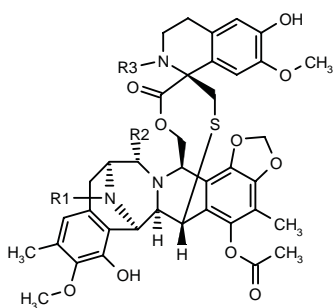
[6*R*-(6α,6αβ,7β,13β,14β,16α,20*R**)]-5-Acetoxy-6',8,14-trihydroxy-7',9-dimethoxy-2',4,10,23-tetramethyl-1',2',3',4',6a,7,12,13,14,16-decahydro-6*H*-spiro[6,16-(epithiopropanoxymethano)-7,13-imino-1,3-dioxolo[7,8]-isoquino[3,2-*b*][3]benzazocine-20,1'-isoquinolin]-19-one

ET-757

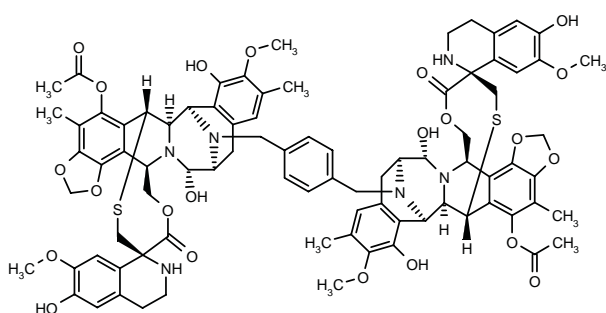


C₄₀H₄₅N₃O₁₁S; Mol wt: 775.8715

ACTION – Semisynthetic ecteinasidin expected to be useful in the treatment of tumors such as melanoma, lung carcinoma and the like. It demonstrated cytotoxic activity up to 50 times better than the natural ecteinasidin-743 (Et-743) against murine leukemia L1210. Other specifically claimed compounds are:



Compound	R1	R2	R3	Formula
Boc-ET-729 [281759]	t-BuOCO	OH	H	C ₄₃ H ₄₉ N ₃ O ₁₃ S
Iso-ET-743 [281760]	H	OH	Me	C ₃₉ H ₄₃ N ₃ O ₁₁ S
Ecteinascidin 875 ET-875 [281765]	Me	CH(CO ₂ Me) ₂	H	C ₄₄ H ₄₉ N ₃ O ₁₄ S



Ecteinascidin 1560 [281767]: C₈₄ H₈₈ N₆ O₂₂ S₂
ET-1560

SOURCE – University of Illinois, Urbana, IL (US).

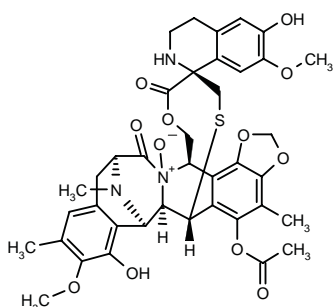
REFERENCES

1. Rinehart, K.L. and Morales, J.J. (University of Illinois) *Semi-synthetic ecteinascidins*. WO 9951238.

ETM-775

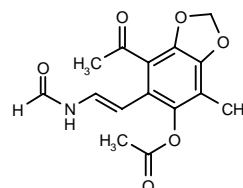
283160

[6*R*-(6 α ,6 β ,7 β ,13 β ,16 α ,20*R*^{*})]-5-Acetoxy-6',8-dihydroxy-7',9-dimethoxy-4,10,23-trimethyl-15-oxido-1',2',3',4',6 α ,7,12,13,14,16-decahydro-6*H*-spiro[6,16-(epithiopropoxymethano)-7,13-imino-1,3-dioxolo-[7,8]isoquino[3,2-*b*][3]benzazocine-20,1'-isoquinolin]-14,19-dione



C₃₉ H₄₁ N₃ O₁₂ S; Mol wt: 775.8279

ACTION – Metabolite of ecteinascidin 743 with an IC₅₀ value of 0.2 μ g/ml for inhibition of the growth of murine leukemia L1210 cells. The antitumor activity of this compound was further assessed against leukemia P388 and human lung carcinoma A549, human colon adenocarcinoma HT-29 and human malignant melanoma MEL-28 (IC₅₀ = 0.01 μ g/ml against all four cell lines). Another compound isolated from the metabolic mixture is:



ETM-305 [283161]: C₁₅ H₁₅ N O₆

SOURCE – Pharma Mar.

REFERENCES

1. Rinehart, K.L. et al. (Pharma Mar, SA) *Metabolites of ecteinascidin 743*. WO 9958125.

ON-5543

281877

Antisense oligonucleotide whose sequence is: 3'-GCTACCGAAAAGGCGGCG-5', in which the linkages between residues 1-2, 2-3, 3-4, 5-6, 13-14, 16-17 and 17-18 are phosphorothioate linkages

ACTION – Partially phosphorothioated antisense oligonucleotide directed against nucleotides 50-67 of the human vitronectin receptor α_v subunit, with the ability to induce apoptosis. Compound was shown to specifically inhibit the expression of integrin α_v subunit in cultured rabbit osteoclasts at 1 μ M, with no effect on β_3 subunit and actin protein levels. In addition, it was shown to inhibit *ex vivo* osteoclast adhesion to glass, bovine bone slices or dentine discs from elephant ivory, as well as bone resorption, at concentrations as low as 0.2 nM, and it also induced apoptosis in cultured osteoclasts. Compound inhibited the adhesion of breast carcinoma MDA-MB-231 cells by about 40% at a concentration of 1 μ M, with induction of apoptosis. Claimed for the treatment or prevention of cancer and cancer metastasis, osteoporosis, ocular diseases, chronic inflammation, psoriasis, restenosis and wound healing.

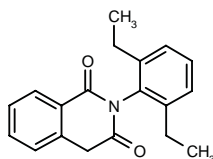
SOURCE – Aventis Pharma.

REFERENCES

1. Uhlmann, E. et al. (Hoechst Marion Roussel Deutschland GmbH) *Antisense oligonucleotides for the inhibition of integrin α_v -subunit expression*. EP 950709, WO 9954456.

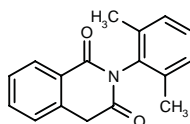
PIQ-22***260570**

2-(2,6-Diethylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione



C19 H19 N O2; Mol wt: 293.3641

ACTION – Antineoplastic agent proven to inhibit tumor cell invasion *in vitro* using murine melanoma B16F10/L5 cells, with almost complete inhibition of invasion (98.9%) at 100 μ M, being more potent than bestatin and actinonin (57.9% and 42.1% inhibition, respectively, at 100 μ M). The mechanism by which compound inhibits metastatic cell invasion appeared to be different from that of the aminopeptidase N (APN) inhibitors bestatin and actinonin, as it was inactive against APN itself, but appeared to inhibit an enzyme possessing greater similarity to puromycin-sensitive aminopeptidase than to APN (APN/PSA-type enzyme); IC_{50} values against this enzyme in MOLT-4 cells were 0.12 μ g/ml for compound and 0.81 and 0.32 μ g/ml, respectively, for bestatin and actinonin. Morphological observations in B16F10/L5 cells showed that compound appeared to inhibit cell extension, suggesting that it could inhibit tumor cell invasion via inhibition of cell mobility. Another related compound is:

**PIQ-11 [281408]:** C17 H15 N O2**SOURCE** – Ishihara Sangyo.**REFERENCES**

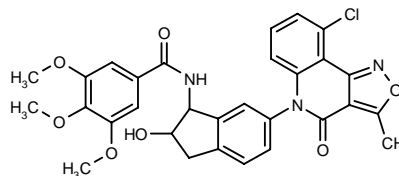
1. Hashimoto, Y. (Ishihara Sangyo Kaisha, Ltd.) *Medicinal compsn.* JP 98109975, WO 9807421.
2. Kagechika, H. et al. *Potent homophthalimide-type inhibitors of B16F10/L5 mouse melanoma cell invasion.* Biol Pharm Bull 1999, 22(9): 1010.
3. Miyachi, H. et al. *Novel potent nonpeptide aminopeptidase N inhibitors with a cyclic imide skeleton.* J Med Chem 1998, 41(3): 263.

*Identified compound **260570** Drug Data Rep 1998, 020(04): 0354.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

281802

N-[6-(9-Chloro-3-methyl-4-oxo-4,5-dihydroisoxazolo-[4,3-c]quinolin-5-yl)-2-hydroxyindan-1-yl]-3,4,5-trimethoxybenzamide

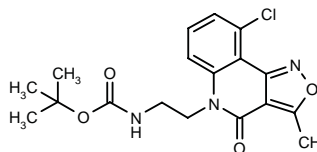


C30 H26 Cl N3 O7; Mol wt: 576.0024

ACTION – Multidrug resistance protein (MRP1) inhibitor with significant activity in reversing MRP1-mediated resistance to doxorubicin, as evaluated in human leukemia HL-60 cells. Potentially useful for treating neoplasms of the Wilm's type, bladder, bone, breast, small cell lung, testicular or thyroid neoplasms, or acute lymphoblastic and myeloblastic leukemia, neuroblastoma, soft tissue sarcoma, Hodgkin's and non-Hodgkin's lymphoma and bronchogenic carcinoma in combination with oncolytic agents selected from doxorubicin, daunorubicin, epirubicin, vincristine and etoposide.

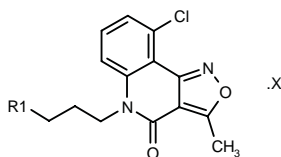
SOURCE – Lilly.**REFERENCES**

1. Gruber, J.M. et al. (Eli Lilly and Company) *Methods for inhibiting MRP1.* WO 9951236.

281803N-[2-(9-Chloro-3-methyl-4-oxo-4,5-dihydroisoxazolo-[4,3-c]quinolin-5-yl)ethyl]carbamic acid *tert*-butyl ester

C18 H20 Cl N3 O4; Mol wt: 377.8260

ACTION – Multidrug resistance protein (MRP1) inhibitor with significant activity in reversing MRP1-mediated resistance to doxorubicin, as evaluated in human leukemia HL-60 cells. Potentially useful for treating neoplasms of the Wilm's type, bladder, bone, breast, small cell lung, testicular or thyroid neoplasms, or acute lymphoblastic and myeloblastic leukemia, neuroblastoma, soft tissue sarcoma, Hodgkin's and non-Hodgkin's lymphoma and bronchogenic carcinoma in combination with oncolytic agents selected from doxorubicin, daunorubicin, epirubicin, vincristine and etoposide. Other representative compounds are:



Compound	R1	X	Formula
281805	t-BuOCONH(CH ₂) ₃		C ₂₂ H ₂₈ ClN ₃ O ₄
281806	(CH ₂) ₃ NH ₂	CF ₃ CO ₂ H	C ₁₇ H ₂₀ ClN ₃ O ₂ .C ₂ H ₃ O ₂
281807	3,4,5-(MeO) ₃ -PhCONHCH ₂		C ₂₄ H ₂₄ ClN ₃ O ₆
281808	CO ₂ H		C ₁₅ H ₁₃ ClN ₂ O ₄
281809	3,4,5-(MeO) ₃ -PhCH ₂ NHCO		C ₂₅ H ₂₆ ClN ₃ O ₆
281810	3,4,5-(MeO) ₃ -PhNHCO(CH ₂) ₃		C ₂₇ H ₃₀ ClN ₃ O ₆

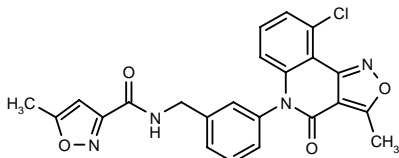
SOURCE – Lilly.

REFERENCES

1. Gruber, J.M. and Norman, B.H. (Eli Lilly and Company) *Methods for inhibiting MRP1*. WO 9951227.

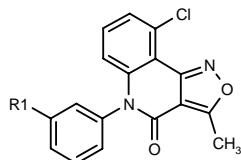
281812

N-[3-(9-Chloro-3-methyl-4-oxo-4,5-dihydroisoxazolo-[4,3-*c*]quinolin-5-yl)benzyl]-5-methylisoxazole-3-carboxamide



C₂₃ H₁₇ Cl N₄ O₄; Mol wt: 448.8643

ACTION – Multidrug resistance protein (MRP1) inhibitor with significant activity in reversing MRP1-mediated resistance to doxorubicin, as evaluated in human leukemia HL-60 cells. Potentially useful for treating neoplasms of the Wilm's type, bladder, bone, breast, small cell lung, testicular or thyroid neoplasms, or acute lymphoblastic and myeloblastic leukemia, neuroblastoma, soft tissue sarcoma, Hodgkin's and non-Hodgkin's lymphoma and bronchogenic carcinoma when combined with oncolytic agents selected from doxorubicin, daunorubicin, epirubicin, vincristine and etoposide. Other representative compounds are:



Compound	R1	Formula
281816	t-BuOCONHCH(CO ₂ H)-CH ₂ CH ₂ CONHCH ₂ CH ₂ O	C ₂₉ H ₃₁ ClN ₄ O ₈
281817	4-MeO-PhNHCOCH ₂	C ₂₆ H ₂₀ ClN ₃ O ₄
281818	4-(NH ₂ SO ₂)-PhCH ₂ NHCH(Me)	C ₂₆ H ₂₃ ClN ₄ O ₄ S
281819	3-indolyl-CONHCH ₂	C ₂₇ H ₁₉ ClN ₄ O ₃
281820	4-OH-PhCH ₂ NH	C ₂₄ H ₁₈ ClN ₃ O ₃
281821	4-(MeSO ₂)-PhCONHCH ₂	C ₂₆ H ₂₀ ClN ₃ O ₅ S
281822	2-Me-5-MeO-PhNHCOCH ₂	C ₂₇ H ₂₂ ClN ₃ O ₄
281823	4-cyclohexyl-PhNHCOCH ₂	C ₃₁ H ₂₈ ClN ₃ O ₃

SOURCE – Lilly.

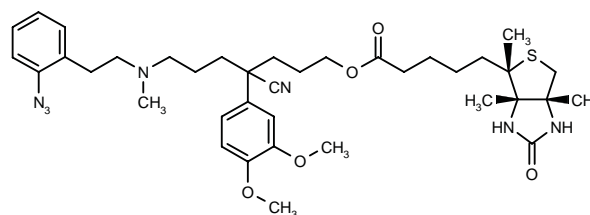
REFERENCES

1. Gruber, J.M. et al. (Eli Lilly and Company) *Methods for inhibiting MRP1*. WO 9951228.

EDP-137

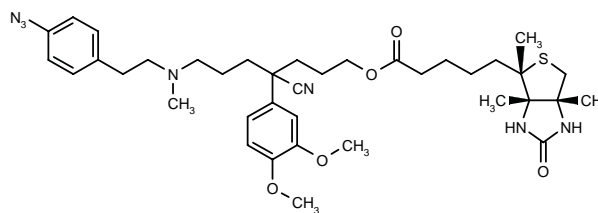
281054

5-[(3*a*S,4*S*,6*a*R)-3*a*,4,6*a*-Trimethyl-2-oxoperhydrothieno[3,4-*d*]imidazol-4-yl]pentanoic acid 7-[*N*-[2-(2-azidophenyl)ethyl]-*N*-methylamino]-4-cyano-4-(3,4-dimethoxyphenyl)heptyl ester



C₃₈ H₅₃ N₇ O₅ S; Mol wt: 719.9467

ACTION – Multidrug resistance (MDR)-reversing agent, a photoactivable biotin-conjugated analogue of verapamil proven to reverse MDR in anthracycline-resistant erythroleukemia K562 cells with identical efficacy to verapamil at slightly higher concentrations. Compound was able to bind irreversibly to P-glycoprotein (P-170 protein). Another biotin-conjugated verapamil analogue is:



EDP-141 [281055]: C₃₈ H₅₃ N₇ O₅ S

SOURCES – Università degli Studi di Firenze, Firenze (IT); Université Paris Nord, Villetaneuse (FR).

REFERENCES

1. Teodori, E. et al. *Synthesis and binding properties of photoactivable biotin-conjugated verapamil derivatives for the study of P-170 glycoprotein*. Bioorg Med Chem 1999, 7(9): 1873.

CHEMOPROTECTIVE AGENTS

MAb 163-93

282382

Murine IgG₁ monoclonal agonist antibody targeting epitopes within the extracellular domain of the human G-CSF receptor

ACTION – Murine monoclonal agonist antibody to the granulocyte colony-stimulating factor (G-CSF) receptor that binds to and interacts with two G-CSF receptor proteins and exerts the same or similar biological effects as native G-CSF. Compound was shown to stimulate the proliferation of murine D4 cells expressing the human G-CSF receptor, as well as tyrosine phosphorylation of kinase JAK2 and transcriptional factor STAT3 in these cells. In addition, it was shown to concentration-dependently stimulate granulocyte colony formation in human and chimpanzee bone marrow cells and to stimulate the proliferation of murine NFS60 cells expressing endogenous mouse G-CSF receptor. Potentially useful for the treatment of neutropenia. Another murine monoclonal agonist antibody is:

Murine IgG_{2a} monoclonal agonist antibody targeting epitopes within the extracellular domain of the human G-CSF receptor

MAb 174-74-11 [282383]

SOURCE – Tanox.

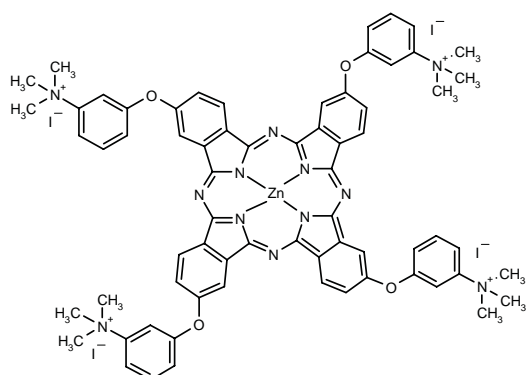
REFERENCES

1. Ni, B. et al. (Tanox, Inc.) *G-CSF receptor agonist antibodies and screening method therefor*. WO 995735.

PHOTODYNAMIC THERAPY

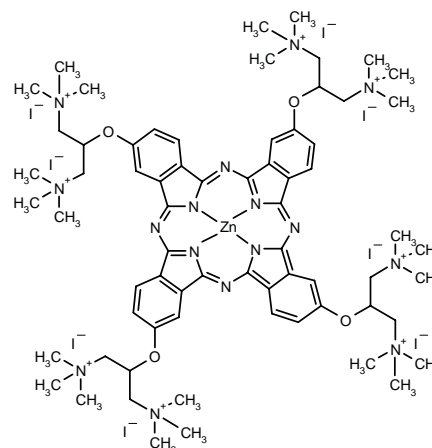
281474

(*SP-4-1*)-[[[3,3',3'',3'''-(29*H*,31*H*-Phthalocyanine-2,9,16,23-tetrayl- κN^{29} , κN^{30} , κN^{31} , κN^{32})tetrakis(oxy)-tetrakis[*N,N,N*-trimethylbenzeneaminiumato]](2-)]zinc(4+) tetraiodide



C68 H64 I4 N12 O4 Zn; Mol wt: 1686.3240

ACTION – Phototherapeutic and photodiagnostic agent with high photodynamic properties, particularly a high molar extinction coefficient and an unusually high value of the singlet oxygen quantum yield, as well as marked absorption in the red region of the visible spectrum, for use as such and in the form of conjugates with macromolecular carrier molecules in the treatment of infectious diseases and conditions characterized by cellular hyperproliferation such as tumors, psoriasis, atheromas, intimal hyperplasia and benign prostatic hyperplasia, as well as for diagnostic purposes. Compound was shown to photoinactivate microorganisms such as *Staphylococcus aureus* ATCC 6538P and *Branhamella catarrhalis* at 1 μ M. Another compound from this series of zinc-phthalocyanines is:



281477: C68 H104 I8 N16 O4 Zn

SOURCE – Molteni.

REFERENCES

1. Roncucci, G. et al. (Molteni L. & C. SpA) *Zinc-phthalocyanines and corresponding conjugates, their preparation and use in photodynamic therapy and as diagnostic agents*. US 5965598.

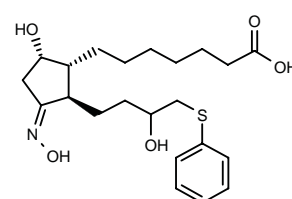
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

281516

7-[5(*S*)-Hydroxy-3-(hydroxyimino)-2(*R*)-[3-hydroxy-4-(phenylsulfanyl)butyl]cyclopent-1(*R*)-yl]heptanoic acid

(15*R,S*)-11-Deoxo-13,14-dihydro-11-(hydroxyimino)-16-(phenylsulfanyl)-17,18,19,20-tetranorprostaglandin D₁



C22 H33 N O5 S; Mol wt: 423.5707

CHEMOPROTECTIVE AGENTS

MAb 163-93

282382

Murine IgG₁ monoclonal agonist antibody targeting epitopes within the extracellular domain of the human G-CSF receptor

ACTION – Murine monoclonal agonist antibody to the granulocyte colony-stimulating factor (G-CSF) receptor that binds to and interacts with two G-CSF receptor proteins and exerts the same or similar biological effects as native G-CSF. Compound was shown to stimulate the proliferation of murine D4 cells expressing the human G-CSF receptor, as well as tyrosine phosphorylation of kinase JAK2 and transcriptional factor STAT3 in these cells. In addition, it was shown to concentration-dependently stimulate granulocyte colony formation in human and chimpanzee bone marrow cells and to stimulate the proliferation of murine NFS60 cells expressing endogenous mouse G-CSF receptor. Potentially useful for the treatment of neutropenia. Another murine monoclonal agonist antibody is:

Murine IgG_{2a} monoclonal agonist antibody targeting epitopes within the extracellular domain of the human G-CSF receptor

MAb 174-74-11 [282383]

SOURCE – Tanox.

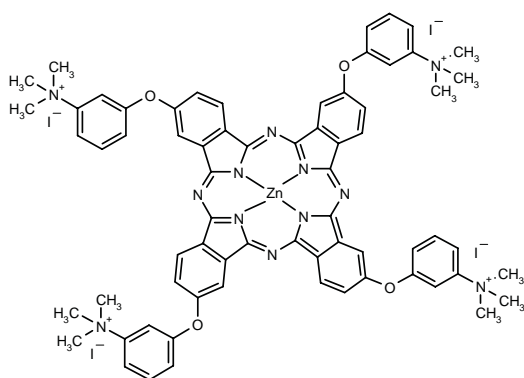
REFERENCES

1. Ni, B. et al. (Tanox, Inc.) *G-CSF receptor agonist antibodies and screening method therefor*. WO 9955735.

PHOTODYNAMIC THERAPY

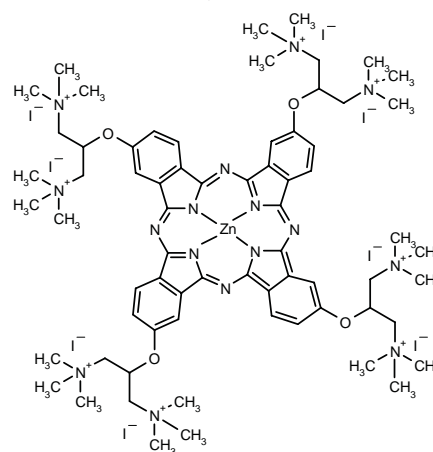
281474

(*SP-4-1*)-[[[3,3',3'',3'''-[(29*H*,31*H*-Phthalocyanine-2,9,16,23-tetrayl- κN^{29} , κN^{30} , κN^{31} , κN^{32})tetrakis(oxy)-tetrakis[*N,N,N*-trimethylbenzeneaminiumato]](2-)]zinc(4+) tetraiodide



C68 H64 I4 N12 O4 Zn; Mol wt: 1686.3240

ACTION – Phototherapeutic and photodiagnostic agent with high photodynamic properties, particularly a high molar extinction coefficient and an unusually high value of the singlet oxygen quantum yield, as well as marked absorption in the red region of the visible spectrum, for use as such and in the form of conjugates with macromolecular carrier molecules in the treatment of infectious diseases and conditions characterized by cellular hyperproliferation such as tumors, psoriasis, atheromas, intimal hyperplasia and benign prostatic hyperplasia, as well as for diagnostic purposes. Compound was shown to photoinactivate microorganisms such as *Staphylococcus aureus* ATCC 6538P and *Branhamella catarrhalis* at 1 μ M. Another compound from this series of zinc-phthalocyanines is:



281477: C68 H104 I8 N16 O4 Zn

SOURCE – Molteni.

REFERENCES

1. Roncucci, G. et al. (Molteni L. & C. SpA) *Zinc-phthalocyanines and corresponding conjugates, their preparation and use in photodynamic therapy and as diagnostic agents*. US 5965598.

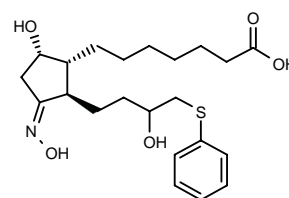
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

281516

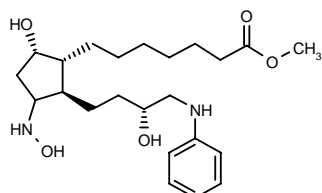
7-[5(*S*)-Hydroxy-3-(hydroxyimino)-2(*R*)-[3-hydroxy-4-(phenylsulfanyl)butyl]cyclopent-1(*R*)-yl]heptanoic acid

(15*R,S*)-11-Deoxo-13,14-dihydro-11-(hydroxyimino)-16-(phenylsulfanyl)-17,18,19,20-tetranorprostaglandin D₁



C22 H33 N O5 S; Mol wt: 423.5707

ACTION – Prostaglandin analogue with potential in the treatment of bone disorders and glaucoma; compound is reported to possess advantages over existing bone disorder therapies by virtue of its ability to increase trabecular number through formation of new trabeculae, increase bone mass and bone volume while maintaining a more normal bone turnover rate, as well as its ability to increase bone formation at the endosteal surface without increasing cortical porosity. Another compound from this series of C11 oxymyl and hydroxylamino prostaglandins is:



281517: C23 H38 N2 O5

SOURCE – Procter & Gamble.

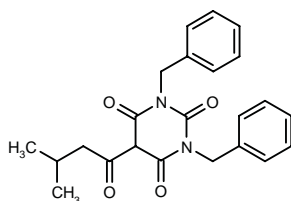
REFERENCES

1. Amburgey, J.S. Jr. et al. (The Procter & Gamble Co.) *C11 oxymyl and hydroxylamino prostaglandins useful as FP agonists*. WO 9950242.

281587

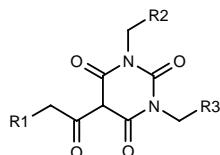
1,3-Dibenzyl-5-(3-methylbutyryl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione

1,3-Dibenzyl-5-(3-methylbutyryl)barbituric acid



C23 H24 N2 O4; Mol wt: 392.4526

ACTION – Bone resorption inhibitor, as demonstrated by 99.2% inhibition of recombinant parathyroid hormone (rPTH)-induced bone resorption in murine femoral and tibial bone preparations at 10 μ M. Other compounds from this series of barbituric acid derivatives include the following:



Compound	R1	R2=R3	Formula
281588	Ph	Ph	C ₂₆ H ₂₂ N ₂ O ₄
281589	2-thienyl	Ph	C ₂₄ H ₂₀ N ₂ O ₄ S
281590	i-Pr	i-Bu	C ₁₉ H ₃₂ N ₂ O ₄

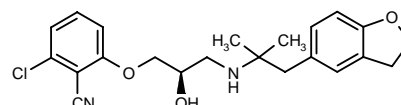
SOURCE – Aventis Pharma.

REFERENCES

1. Sakai, K. and Satoh, Y. (Hoechst Marion Roussel, SA) *Barbituric acid deriv. and preventive and therapeutic agent for bone and cartilage containing the same*. JP 99279157, WO 9950252.

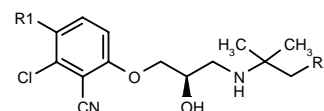
281835

2-Chloro-6-[3-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,1-dimethylethylamino]-2(*R*)-hydroxypropoxy]benzonitrile



C22 H25 Cl N2 O3; Mol wt: 400.9035

ACTION – Calcilytic compound useful as a calcium receptor antagonist, with potential in the treatment of diseases associated with abnormal bone or mineral homeostasis such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and osteoporosis. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
281836	H	3-quinoliny	C ₂₃ H ₂₄ ClN ₃ O ₂
281837	H	2-quinoliny	C ₂₃ H ₂₄ ClN ₃ O ₂
281838	H	3-isoquinoliny	C ₂₃ H ₂₄ ClN ₃ O ₂
281839	H	2-Pyr-CH ₂ CH ₂	C ₂₁ H ₂₆ ClN ₃ O ₂
281840	4-morpholinyl-SO ₂ NH	2-Pyr-CH ₂ CH ₂	C ₂₈ H ₃₄ ClN ₅ O ₅ S
281841	H	3-Pyr-CH ₂ CH ₂	C ₂₁ H ₂₆ ClN ₃ O ₂
281842	4-morpholinyl-SO ₂ NH	3-Pyr-CH ₂ CH ₂	C ₂₈ H ₃₄ ClN ₅ O ₅ S
281843	H	4-Et-2-Pyr	C ₂₁ H ₂₆ ClN ₃ O ₂

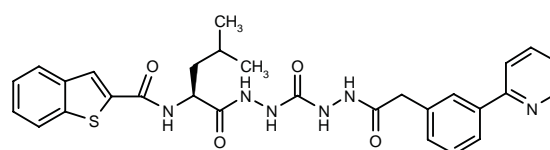
SOURCES – NPS Pharmaceuticals; SmithKline Beecham.

REFERENCES

1. Bhatnagar, P.K. et al. (SmithKline Beecham Corp.; NPS Pharmaceuticals, Inc.) *Calcilytic cpds. and methods of use*. WO 9951241.

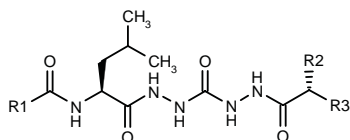
283618

*N*²-(*N*-Benzothiophen-2-ylcarbonyl-L-leucyl)-*N*^{2'}-[2-[3-(2-pyridinyl)phenyl]acetyl]carbonohydrazide



C29 H30 N6 O4 S; Mol wt: 558.6600

ACTION – An inhibitor of proteases including cysteine proteases of the cathepsin family, most particularly cathepsin K, and therefore useful in the treatment of disorders associated with excessive bone or cartilage loss, e.g., osteoporosis, periodontitis and arthritis. Other specifically claimed diacylcarbohydrazide compounds are:



Compound	R1	R2	R3	Formula
283619	5-Cl-2-benzofuryl	3-(2-Pyr)-Ph	H	C ₂₉ H ₂₉ ClN ₆ O ₅
283620	3-I-4-MeO-Ph	3-I-4-MeO-PhCONH	i-Bu	C ₂₉ H ₃₈ I ₂ N ₆ O ₇

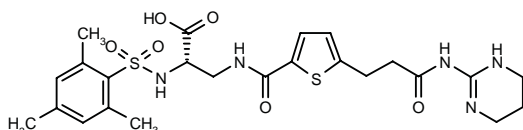
SOURCE – SmithKline Beecham.

REFERENCES

1. Halbert, S.M. et al. (SmithKline Beecham Corp.) *Protease inhibitors*. WO 9959570.

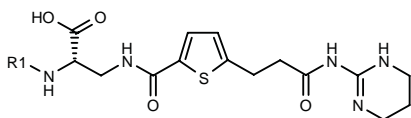
283622

3-[5-[2-[N-(1,4,5,6-Tetrahydropyrimidin-2-yl)carbamoyl]ethyl]thien-2-ylcarboxamido]-2(S)-(2,4,6-trimethylphenylsulfonamido)propionic acid



C₂₄ H₃₁ N₅ O₆ S₂; Mol wt: 549.6699

ACTION – Bone resorption inhibitor that acts by inhibiting the vitronectin $\alpha_v\beta_3$ receptor. Compound gave IC₅₀ values for inhibition of kistrin binding to the human vitronectin receptor and for inhibition of binding of 293 cells to human vitronectin of 0.0015 and 0.010 μ M, respectively. Particularly useful for the treatment of bone disorders including osteoporosis, hypercalcemia, osteopenia, dental disorders, hyperparathyroidism, periarticular erosion in rheumatoid arthritis and Paget's disease. Other exemplified thienyl substituted acylguanidines include the following:



Compound	R1	Formula
283623	1-adamantyl-CH ₂ OCO	C ₂₇ H ₃₇ N ₅ O ₆ S
283624	1-Naph-SO ₂	C ₂₅ H ₂₇ N ₅ O ₆ S ₂
283625	4-Cl-PhSO ₂	C ₂₁ H ₂₄ ClN ₅ O ₆ S ₂
283626	4-Ph-PhSO ₂	C ₂₇ H ₂₉ N ₅ O ₆ S ₂
283627	4-CF ₃ -PhSO ₂	C ₂₂ H ₂₄ F ₃ N ₅ O ₆ S ₂
283628	SO ₂ (CH ₂) ₃ Cl	C ₁₈ H ₂₆ ClN ₅ O ₆ S ₂
283629	4-t-Bu-PhSO ₂	C ₂₅ H ₃₃ N ₅ O ₆ S ₂
283630	4-i-Pr-PhSO ₂	C ₂₄ H ₃₁ N ₅ O ₆ S ₂

SOURCES – Aventis Pharma; Genentech.

REFERENCES

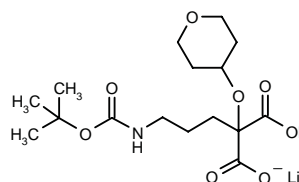
1. Scheunemann, K.-H. et al. (Hoechst Marion Roussel Deutschland GmbH; Genentech, Inc.) *Thienyl subst. acylguanidines as inhibitors of bone resorption and vitronectin receptor antagonists*. EP 960882, WO 9959992.

DF-1601A

281035

5-(*tert*-Butoxycarbonylamino)-2-carboxy-2-(tetrahydropyran-4-yloxy)pentanoic acid lithium salt

2-[3-(*tert*-Butoxycarbonylamino)propyl]-2-(tetrahydropyran-4-yloxy)propanedioic acid lithium salt



C₁₆ H₂₆ Li N O₈; Mol wt: 367.3214

ACTION – Orally active bone-sparing agent, a tartronic acid (tartronate) derivative able to inhibit bone resorption and stimulate mineralization. It exhibited anabolic effects on rat calvarial osteoblasts, in contrast to alendronate. *In vivo*, compound (30 mg/kg/day p.o. for 21 or 28 days) was able to restore bone density in two mouse models of osteoporosis: osteopenia induced by ovariectomy or by orchietomy. In a model of low-turnover osteopenia in rats, compound at doses of 3 and 10 mg/kg/day p.o. for 3 months significantly increased bone mass density in proximal metaphysis, proximal epiphysis and diaphysis. Potentially useful for the treatment of osteopenic disorders.

SOURCE – Dompé.

REFERENCES

1. Allegretti, M. et al. (Dompé Farmaceutici SpA) *Geminal carboxylic acids and esters thereof pharmaceutical formulations containing them useful in the treatment of bone dysmetabolism*. EP 792878, US 5908863.

2. Caselli, G.F. et al. *Tartronic acid derivatives have anabolic effects on osteoblasts*. J Bone Miner Res 1999, 14(Suppl. 1): Abst SU144.

3. Chiusaroli, R. et al. *The new tartronate DF 1601A given by the oral route restores bone mass in the aged ovariectomized rat*. J Bone Miner Res 1999, 14(Suppl. 1): Abst SU371.

4. Mosca, M. et al. *DF 1601A, a new tartronate derivative orally active in osteopenic models in mice*. J Bone Miner Res 1999, 14(Suppl. 1): Abst 1192.

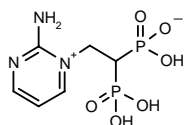
LIPOSOMAL ISA-13-1²

281915

Liposome-encapsulated ISA-13-1 in negatively charged DSPG:cholesterol (67:33) liposomes

ISA-13-1^{*,1-3}
249422

2-(2-Aminopyrimidin-1-yl)ethylidenediphosphonic acid inner salt



C6 H11 N3 O6 P2; Mol wt: 283.1190

ACTION – Agent for the treatment of osteoporosis, a bisphosphonate with improved solubility of the calcium salt and oral absorption compared to alendronate and pamidronate. Compound showed reduced stability of the calcium complex and lower affinity for hydroxyapatite compared to alendronate, but exerted a comparable beneficial effect on bone volume and bone osteolysis in rats after daily i.m. administration of 0.01 mg/kg for 14 days. In the Walker carcinosarcoma tumor osteolysis model in rats, s.c. administration of ISA-13-1 or alendronate (50 µmol/kg/day s.c. for 3 days) also produced comparable inhibition of osteoclast activity and bone resorption. Encapsulation of compound in liposomes enhanced the growth-inhibitory potency on murine macrophage RAW 264 cells compared to free drug (IC_{50} = 1.8 and 196 µM, respectively). Significantly lower levels of the compound were detected in the intestinal wall following oral administration in rats and it had no deleterious effect on the tight junctions of intestinal tissue, suggesting potentially reduced toxic effects on the gastrointestinal tract.

SOURCE – Yissum.

REFERENCES

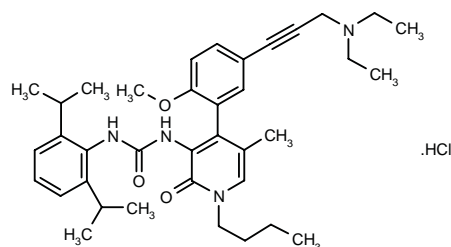
1. Alferiev, I.S. et al. (Yissum Research Development Co.) *Novel bisphosphonates, process for their preparation and pharmaceutical compsns. containing them*. WO 9708178.
2. Cohen, H. et al. *Synthesis and preclinical pharmacology of 2-(2-aminopyrimidin-1-yl)ethylidene-1,1-bisphosphonic acid betaine (ISA-13-1) - A novel bisphosphonate*. Pharm Res 1999, 16(9): 1399.
3. Hoffman, A. et al. *Improved bioavailability of novel bisphosphonates*. Pharm Res 1995, 12(9, Suppl.): Abst PPDM 8394.

*Identified compound 249422 Drug Data Rep 1997, 019(07): 0666.

TREATMENT OF LIPOPROTEIN DISORDERS

282108

*N*¹-(2,6-Diisopropylphenyl)-*N*³-[1-butyl-4-[5-[3-(diethylamino)-1-propynyl]-2-methoxyphenyl]-5-methyl-2-oxo-1,2-dihydropyridin-3-yl]urea hydrochloride



C37 H50 N4 O3 . HCl; Mol wt: 635.2879

ACTION – Hypolipidemic and antiarteriosclerotic agent, an ACAT inhibitor that exhibits higher potency against enzyme from rat macrophages (IC_{50} = 16 nM) than against enzyme from rabbit liver microsomes (IC_{50} = 295 nM).

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Muraoka, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Pyridone derivs. and process for producing the same*. WO 9943659.

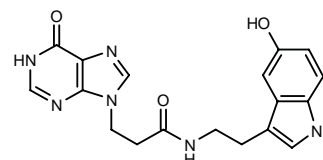
TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

AIT-202

282838

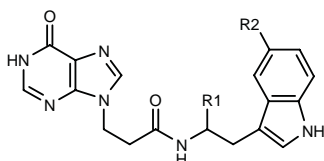
N-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-3-(6-oxo-6,9-dihydro-1*H*-purin-9-yl)propionamide

N-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-3-(hypoxanthin-9-yl)propionamide



C18 H18 N6 O3; Mol wt: 366.3792

ACTION – Monoamine oxidase (MAO) inhibitor (IC_{50} ~ 2.0 µM) with the ability to efficiently cross the blood-brain barrier. It has been found to have a beneficial effect on body weight in obese mice and to reduce total serum cholesterol and increase HDL cholesterol levels in mice following oral administration. This compound is thus considered to be potentially useful as an antiobesity agent and for treating lipid disorders. Other specifically claimed 9-substituted hypoxanthine derivatives are:



Compound	R1	R2	Formula
AIT-072 [282839]	H	H	C ₁₈ H ₁₈ N ₆ O ₂
AIT-111 [282840]	CO ₂ H	OH	C ₁₉ H ₁₈ N ₆ O ₅

SOURCE – NeoTherapeutics.

REFERENCES

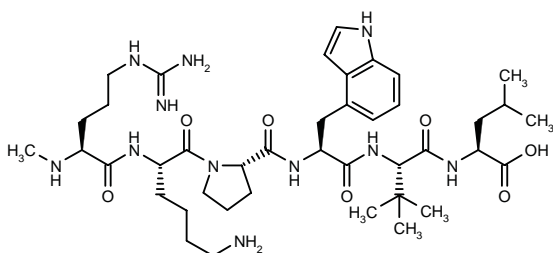
1. Glasky, A.J. (NeoTherapeutics, Inc.) *Novel serotonin-like 9-subst. hypoxanthine and methods of use*. WO 9957120.

NT69L

282134

N-Methyl-L-arginyl-L-lysyl-L-prolyl-L-*neo*-tryptophyl-L-*tert*-leucyl-L-leucine

N-Methyl-L-arginyl-L-lysyl-L-prolyl-L-(4-indolyl)alanyl-L-*tert*-leucyl-L-leucine



C41 H67 N11 O7; Mol wt: 826.0503

ACTION – Neurotensin polypeptide analogue containing a novel amino acid, *L*-*neo*-tryptophan, that interacts with neurotensin receptors and is useful for inducing a neurotensin response. Compound exhibited high affinity for neurotensin receptors ($K_d = 1.55 \pm 0.09$ and 0.82 ± 0.07 nM, respectively, for human and rat NTR-1 receptors cloned in CHO-K1 cells) and was shown to stimulate phosphatidyl inositol (PI) turnover in CHO-K1 cells expressing human and rat NTR-1 with respective EC_{50} values of 2.3 ± 0.5 and 1.34 ± 0.02 nM. Compound exhibited greatly increased resistance to peptidases as compared to neurotensin ($t_{1/2} = 500$ h vs. 1.9 h in human plasma). Compound was shown to induce antinociception in the hot-plate assay and hypothermia in rats with ED_{50} values of 0.3 and 0.4 mg/kg i.p. at 90 min, respectively. Compound was also shown to prevent apomorphine-induced climbing behavior ($ED_{50} = 16$ µg/kg i.p.) and to reverse haloperidol-induced catalepsy ($ED_{50} = 260$ µg/kg i.p.) in rats. In addition, it was found to cause significant reductions in body weight and food intake when administered i.p. to both normal and genetically obese rats.

SOURCE – Mayo Foundation, Rochester, MN (US).

REFERENCES

1. Richelson, E. et al. (Mayo Foundation for Medical Education and Research) *Neo-tryptophan*. WO 9952539.

RECOMBINANT METHIONYL HUMAN LEPTIN

281804

r-metHuLeptin

ACTION – Antiobesity agent, a recombinant methionyl human leptin proven to induce weight loss (0.7-7.1 kg at 24 weeks) and body fat loss (> 95% of body weight loss was fat loss) when administered s.c. at doses of 0.01-0.3 mg/kg to obese adult individuals. Compound showed an acceptable short-term (6 months or less) safety profile.

SOURCE – Amgen.

REFERENCES

1. Heymsfield, S.B. et al. *Recombinant leptin for weight loss in obese and lean adults. A randomized, controlled, dose-escalation trial*. JAMA - J Am Med Assoc 1999, 282(16): 1568.

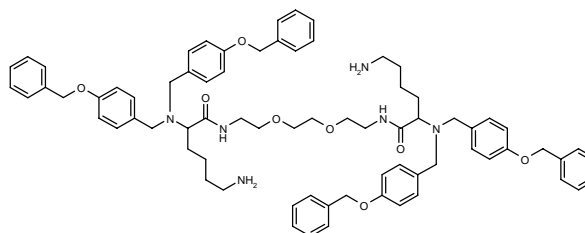
2. Mallard, S. et al. *Pharmacokinetics and efficacy of recombinant human leptin formulated in a calcium-alginate gel, in male Sprague-Dawley rats*. Annu Meet Am Assoc Pharm Sci (Nov 14-18, New Orleans) 1999, Abst 2238.

3. Mallard, S.P. et al. *Pharmacokinetics of recombinant methionyl human leptin (r-metHuLeptin) in male CD-1 mice*. Pharm Res 1997, 14(11, Suppl.): S78.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

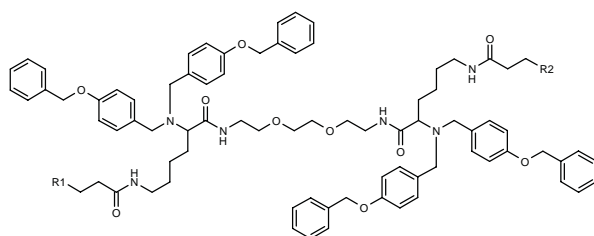
282376

N,N'-(Ethylenedioxy)bis(ethylene)bis[6-amino-2-[*N,N*-bis(4-benzyloxybenzyl)amino]hexanamide]



C74 H88 N6 O8; Mol wt: 1189.5430

ACTION – Small-molecule compound that binds to the erythropoietin (EPO) receptor and competes with the natural ligand for binding to this receptor. Potentially useful for stimulating red blood cell production without the immune response associated with large peptides, and with the advantage of oral activity. Other specifically claimed substituted amino acids are:



Compound	R1=R2	Formula
282377	CO ₂ H	C ₆₂ H ₉₆ N ₆ O ₁₄
282378	CH ₂ CO ₂ H	C ₆₄ H ₁₀₀ N ₆ O ₁₄

SOURCE – Ortho-McNeil.

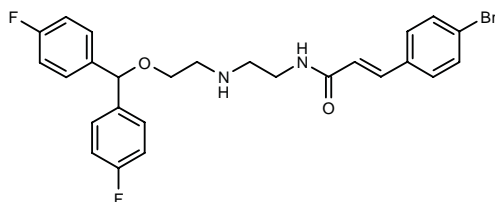
REFERENCES

1. Connolly, P. and Murray, W. (Ortho-McNeil Pharmaceutical, Inc.) *Subst. amino acids as erythropoietin mimetics*. WO 9954279.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

280312

N-[2-[2-[Bis(4-fluorophenyl)methoxy]ethylamino]ethyl]-3-(4-bromophenyl)-2(*E*)-propenamide



C₂₆ H₂₅ Br F₂ N₂ O₂; Mol wt: 515.3955

ACTION – Potential cocaine antagonist, a dopamine transporter (DAT) inhibitor with comparable DAT binding affinity to cocaine (K_i = 510 and 759 nM, respectively) and reduced potency for [³H]-dopamine reuptake inhibition (IC_{50} = 1380 and 190 nM, respectively), and moderate to high selectivity over the norepinephrine (NE) transporter (K_i = 1760 nM) and NE reuptake (IC_{50} > 10 μ M). *In vivo*, it suppressed spontaneous locomotor activity in mice with an ED_{50} of 47.4 mg/kg i.p. and it attenuated cocaine-induced stimulation of locomotor activity with an ED_{50} of 60 mg/kg i.p. Suggested to represent a good lead compound for further SAR studies to develop a potent and selective cocaine antagonist useful for the treatment of cocaine abuse.

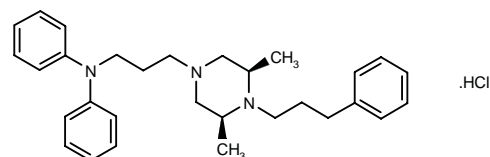
SOURCES – Massachusetts General Hospital, Boston, MA (US); Northeastern University, Boston, MA (US).

REFERENCES

1. Choi, S.-W. et al. *Design, synthesis, and biological evaluation of novel non-piperazine analogues of 1-[2-(diphenylmethoxy)ethyl]- and 1-[2-bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazines as dopamine transporter inhibitors*. J Med Chem 1999, 42(18): 3647.

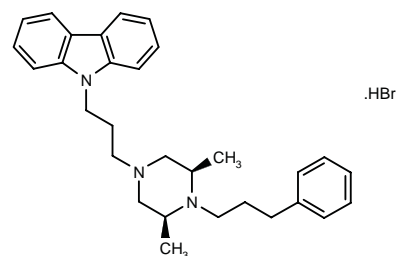
281758

cis-N-[3-[3,5-Dimethyl-4-(3-phenylpropyl)piperazin-1-yl]propyl]-*N,N*-diphenylamine hydrochloride



C₃₀ H₃₉ N₃ . HCl; Mol wt: 478.1200

ACTION – Potent and highly selective dopamine transporter (DAT) ligand (IC_{50} = 61 nM against [³H]-Win-35428 binding) with less activity at the 5-HT (IC_{50} = 219 nM against [³H]-paroxetine binding) and norepinephrine transporters (IC_{50} = 3640 nM against [³H]-nisoxetine binding). Compound also showed some selectivity for σ_1 -over σ_2 -receptors (K_i = 97.2 and 183 nM, respectively). In comparison to the parent compound rimcazole, it was more potent and more selective against both DAT (K_i = 224 nM) and σ_1 -receptors (K_i = 908 nM). In rats, it did not demonstrate cocaine-like behavioral effects. Potentially useful for the treatment of cocaine abuse. Another rimcazole analogue selected for further study is:



281756: C₃₀ H₃₇ N₃ . HBr

SOURCES – National Institute on Drug Abuse, Bethesda, MD (US); National Institutes of Health, Bethesda, MD (US).

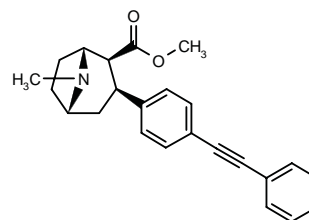
REFERENCES

1. Husbands, S.M. et al. *Structure-activity relationships at the monoamine transporters and sigma receptors for a novel series of 9-[3-(cis-3,5-dimethyl-1-piperazinyl)-propyl]carbazole (rimcazole) analogues*. J Med Chem 1999, 42(21): 4446.

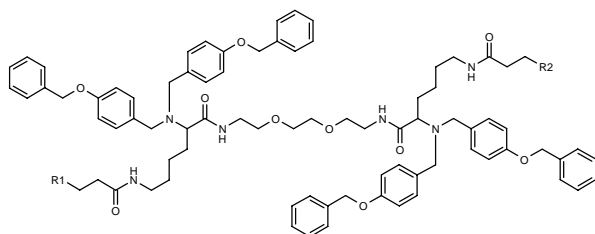
RTI-4229-298

283722

(1*R*,2*S*,3*S*,5*S*)-8-Methyl-3-[4-(phenylethynyl)phenyl]-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester



C₂₄ H₂₅ N O₂; Mol wt: 359.4665



Compound	R1=R2	Formula
282377	CO ₂ H	C ₈₂ H ₉₆ N ₆ O ₁₄
282378	CH ₂ CO ₂ H	C ₈₄ H ₁₀₀ N ₆ O ₁₄

SOURCE – Ortho-McNeil.

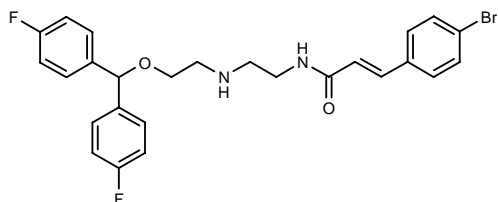
REFERENCES

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TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

280312

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C₂₆ H₂₅ Br F₂ N₂ O₂; Mol wt: 515.3955

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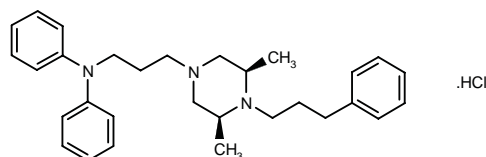
SOURCES – Massachusetts General Hospital, Boston, MA (US); Northeastern University, Boston, MA (US).

REFERENCES

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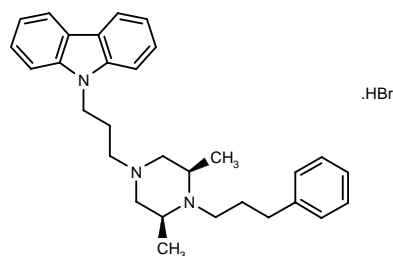
281758

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C₃₀ H₃₉ N₃ . HCl; Mol wt: 478.1200

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SOURCES – National Institute on Drug Abuse, Bethesda, MD (US); National Institutes of Health, Bethesda, MD (US).

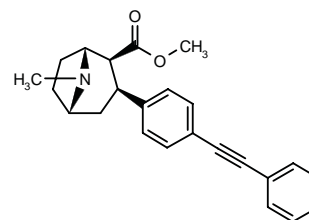
REFERENCES

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RTI-4229-298

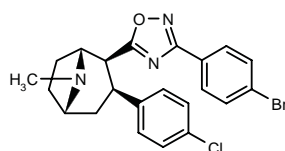
283722

(1*R*,2*S*,3*S*,5*S*)-8-Methyl-3-[4-(phenylethynyl)phenyl]-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester



C₂₄ H₂₅ N O₂; Mol wt: 359.4665

ACTION – Compound with high affinity for cocaine binding sites in the brain, particularly the dopamine and 5-HT transporter sites, giving IC_{50} values of 3.7 ± 0.16 , 46.8 ± 5.8 and 346.6 ± 25 nM for inhibition of radioligand binding to the dopamine, 5-HT and norepinephrine sites, respectively. It showed a slow onset and a long duration of action, in addition to a slow rate of entry into the brain, making it particularly well suited as a substitute medication for psychostimulant abuse, as well as for the treatment of Parkinson's disease or depression. Another specifically claimed tropane derivative is:



283723: C22 H21 Br Cl N3 O

SOURCE – Research Triangle Institute, Research Triangle Park, NC (US).

REFERENCES

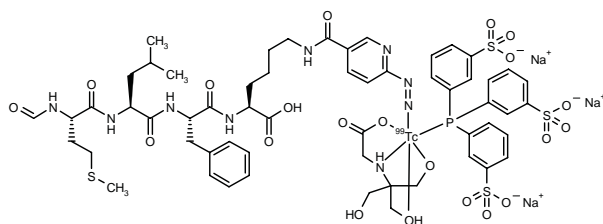
1. Carroll, F.I. et al. (Research Triangle Institute) *Cocaine receptor binding ligands*. WO 9961023.

DIAGNOSTIC AGENTS

RP-463

281994

Trisodium (OC-6-54)-[N-formyl-L-methionyl-L-leucyl-L-phenylalanyl-N⁶-[6-(diazenyl-κN²)pyridin-3-ylcarbonyl]-L-lysinate(2-)] [N-[2-hydroxy-1,1-bis(hydroxy-κO-methyl)ethyl]glycinato-κN,κO][[3,3',3''-(phosphinidyl-κP)tris[benzenesulfonato]](3-)]technetate(3-)-99Tc



C57 H68 N9 Na3 O21 S4 Tc ; Mol wt: 1542.4140

ACTION – A stabilized ternary ligand technetium-99m complex of a hydrazino nicotinamide-derivatized chemotactic peptide (fMLFK-HYNIC) useful for infection imaging. Compound was able to inhibit [³H]-fMLF binding in polymorphonuclear leukocytes (PMNs; $IC_{50} = 2$ nM) and to induce superoxide release in PMNs ($EC_{50} = 0.2$ nM), like unlabeled peptide fMLFK-HYNIC ($IC_{50} = 3$ nM). *In vivo* in rabbits infected with *Escherichia coli*, RP-463 was cleared rapidly from blood and excreted mainly via the renal system. The Tc-99m-labeled complex rapidly accumulated at the site of infection, its uptake increasing over time, resulting in target-to-background ratios of 1.5 ± 0.2 at 15 min and of 7.5 ± 0.4 at 4 h after injection. Infectious foci could be visualized clearly as soon as 2 h

after injection of RP-463. However, a transient decrease (35%) in white blood cell count was detected after injection of RP-463 and it is suggested that further research should concentrate on the development of potent antagonists of chemotactic peptide receptor or other receptors in PMNs and monocytes.

SOURCES – AnorMED; DuPont Pharmaceuticals; McNeil Consumer Products.

REFERENCES

1. Edwards, D.S. et al. *RP463: A stabilized technetium-99m complex of a hydrazino nicotinamide derivatized chemotactic peptide for infection imaging*. *Bioconjugate Chem* 1999, 10(5): 884.

LIPOSOMAL MnBOPP⁴

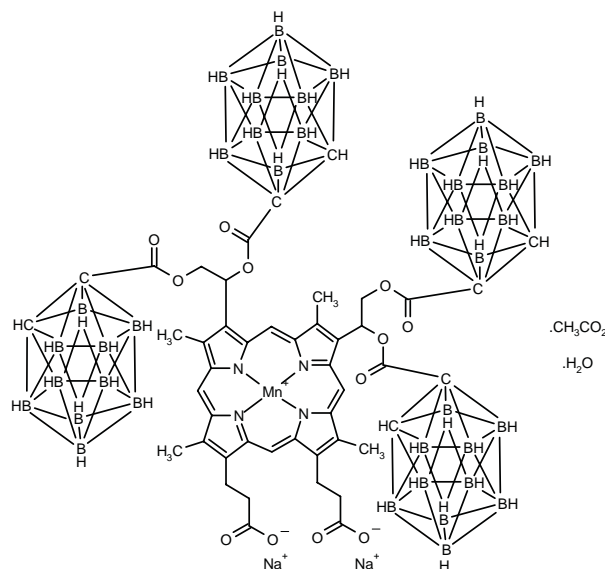
281890

Liposome-encapsulated MnBOPP

MnBOPP¹⁻⁴

281431

Disodium [7,12-Bis[1,2-bis[(1,2-dicarbadodecaboran(12)-1-ylcarbonyl)oxy]-3,8,13,17-tetramethyl-21H,23H-porphine-2,18-dipropionato(4-)]manganate(1-) acetate hydrate

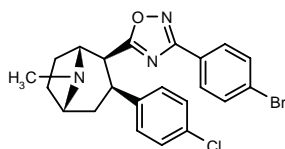


C46 H74 B40 Mn N4 Na2 O12 . C2 H3 O2 . H2O

ACTION – Liposomal formulation of the manganese chelate of BOPP (MnBOPP), a contrast agent for magnetic resonance imaging (MRI) and a radiation sensitizer for boron neutron capture therapy, proven to selectively localize in rat gliosarcoma 9L and preferentially enhance the tumor-normal brain contrast of T1-weighted images for at least 92 h. The liposomal formulation was much better tolerated than the free drug in mice, and appeared to provide a means to administer high doses of free drug with reduced toxicity.

SOURCES – University of California, San Francisco, San Francisco, CA (US); Roswell Park Cancer Institute, Buffalo, NY (US); State University of New York, Buffalo, Buffalo, NY (US).

ACTION – Compound with high affinity for cocaine binding sites in the brain, particularly the dopamine and 5-HT transporter sites, giving IC_{50} values of 3.7 ± 0.16 , 46.8 ± 5.8 and 346.6 ± 25 nM for inhibition of radioligand binding to the dopamine, 5-HT and norepinephrine sites, respectively. It showed a slow onset and a long duration of action, in addition to a slow rate of entry into the brain, making it particularly well suited as a substitute medication for psychostimulant abuse, as well as for the treatment of Parkinson's disease or depression. Another specifically claimed tropane derivative is:



283723: C22 H21 Br Cl N3 O

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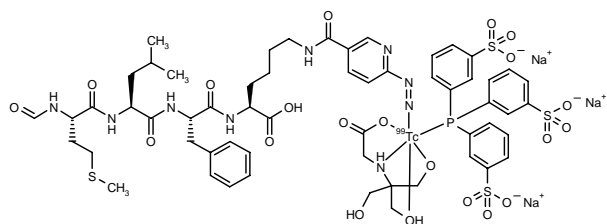
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RP-463

281994

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LIPOSOMAL MnBOPP⁴

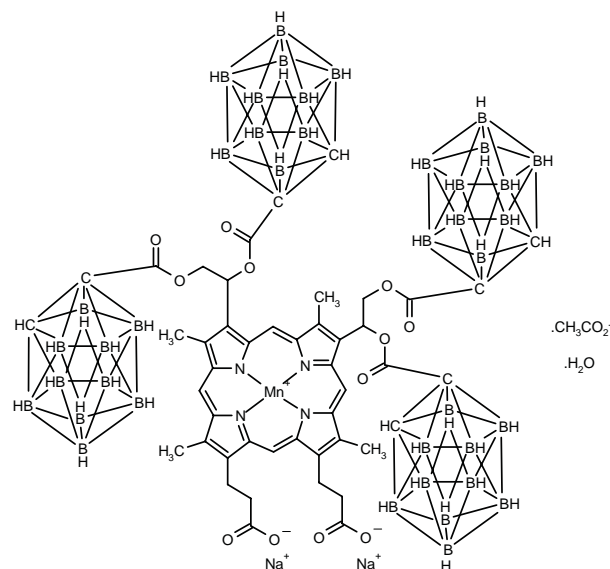
281890

Liposome-encapsulated MnBOPP

MnBOPP¹⁻⁴

281431

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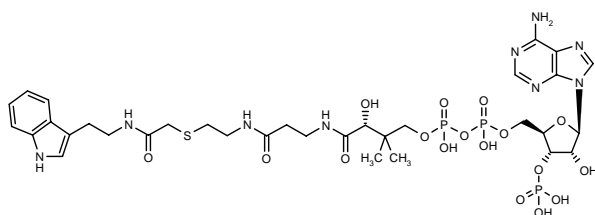
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2. Kahl, S.B. and Koo, M.-S. (University of California, Oakland) *Boronated metalloporphyrins and therapeutic methods.* WO 9509856.
3. Huang, L.R. et al. *Boronated metalloporphyrins: A novel aproach to the diagnosis and treatment of cancer using contrast-enhanced MR imaging and neutron capture therapy.* J Magn Reson Imaging 1993, 3(2): 351.
4. Zhou, R. et al. *Biopharmaceutics of boronated-radiosensitizers: Liposomal formulation of MnBOPP (manganese chelate of 2,4-(α,β -dihydroxyethyl)deuterioporphyrin IX) and comparative toxicity in mice.* J Pharm Sci 1999, 88(9): 912.

PHARMACOLOGICAL TOOLS

283180

S-[N-[2-(Indol-3-yl)ethyl]carbamoylmethyl]coenzyme A



C33 H48 N9 O17 P3 S; Mol wt: 967.7762

ACTION – Serotonin–melatonin pathway modulator that acts by inhibiting aralkylamine *N*-acetyltransferase (also known as serotonin acetyltransferase and serotonin acetylase; $IC_{50} = 150$ nM). A synthetic bisubstrate compound incorporating the indole and coenzyme A moieties of the two substrates (tryptamine and acetyl-CoA), it is potentially useful as a tool for elucidating the biological functions of melatonin and pineal serotonin, and possibly also as a therapeutic agent.

The enzyme catalyzes the conversion of serotonin to *N*-acetylserotonin, which is the immediate precursor of melatonin, in the pineal gland.

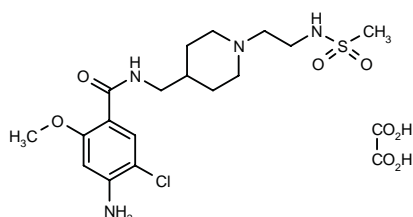
SOURCE – Rockefeller University, New York, NY (US).

REFERENCES

1. Cole, P.A. and Khalil, E. (Rockefeller University) *Inhibitors of serotonin N-acetyltransferase.* US 5990094.

280685

4-Amino-5-chloro-2-methoxy-*N*-[1-[2-(methylsulfonylamido)ethyl]piperidin-4-ylmethyl]benzamide oxalate



C17 H27 Cl N4 O4 S . C2 H2 O4; Mol wt: 508.9771

M.p. 177-8 °C (*decomp.*).

ACTION – Potent and selective 5-HT₄ receptor agonist ($ED_{50} = 7.0$ nM in guinea pig ascending colon) with nanomolar affinity for the 5-HT₄ receptor ($K_i = 9.6$ nM for displacement of [³H]-GR-113808 binding from guinea pig striatum) and high selectivity over a series of receptors including 5-HT_{1A}, 5-HT₂, 5-HT₃ and dopamine D₂ receptors and α_1 -adrenoceptors ($K_i > 1000$ nM). Potentially useful as a pharmacological tool for studying 5-HT₄ receptor function *in vivo*.

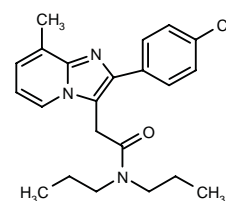
SOURCE – Yoshitomi (Welfide).

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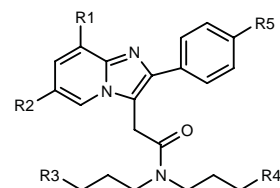
280782

2-[2-(4-Chlorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl]-*N,N*-dipropylacetamide



C22 H26 Cl N3 O; Mol wt: 383.9204

ACTION – High-affinity ligand for the peripheral benzodiazepine site on the GABA_A receptor complex ($pIC_{50} = 8.85$ and 8.55 for cortex and ovarian receptors, respectively) with high selectivity over the central benzodiazepine receptor site ($pIC_{50} = 2.4$). *In vivo*, at a dose of 25 mg/kg i.p., it significantly increased both plasma and brain concentrations of neuroactive steroids including pregnenolone, progesterone, allopregnanolone and allotetrahydrodeoxycorticosterone by 126, 103, 85 and 83%, respectively, in plasma and 87, 101, 73 and 50%, respectively, in cerebral cortex. Potentially useful as a pharmacological tool for understanding the pharmacology and physiology of peripheral benzodiazepine receptor sites. Other 2-phenylimidazo[1,2-a]pyridine derivatives include the following:



Compound	R1	R2	R3=R4	R5	Formula
280781	H	CO ₂ Me	H	H	C ₂₃ H ₂₇ N ₃ O ₃
280783	Cl	H	H	Cl	C ₂₁ H ₂₃ Cl ₂ N ₃ O
280784	H	H	Me	H	C ₂₃ H ₂₉ N ₃ O

SOURCES – Università di Bari, Bari (IT); Università degli Studi di Cagliari, Cagliari (IT).

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1. Trapani, G. et al. *Novel 2-phenylimidazo[1,2-a]pyridine derivatives as potent and selective ligands for peripheral benzodiazepine receptors: Synthesis, binding affinity, and in vivo studies.* J Med Chem 1999, 42(19): 3934.

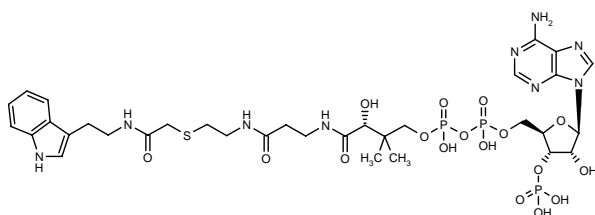
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1. Kahl, S.B. and Craik, C.S. (Universität Regensburg; University of California, Oakland) *Metallo porphyrin compsns.* JP 96501103, WO 9405285.
2. Kahl, S.B. and Koo, M.-S. (University of California, Oakland) *Boronated metalloporphyrins and therapeutic methods.* WO 9509856.
3. Huang, L.R. et al. *Boronated metalloporphyrins: A novel aproach to the diagnosis and treatment of cancer using contrast-enhanced MR imaging and neutron capture therapy.* J Magn Reson Imaging 1993, 3(2): 351.
4. Zhou, R. et al. *Biopharmaceutics of boronated-radiosensitizers: Liposomal formulation of MnBOPP (manganese chelate of 2,4-(α,β -dihydroxyethyl)deuterioporphyrin IX) and comparative toxicity in mice.* J Pharm Sci 1999, 88(9): 912.

PHARMACOLOGICAL TOOLS

283180

S-[N-[2-(Indol-3-yl)ethyl]carbamoylmethyl]coenzyme A



C33 H48 N9 O17 P3 S; Mol wt: 967.7762

ACTION – Serotonin–melatonin pathway modulator that acts by inhibiting aralkylamine *N*-acetyltransferase (also known as serotonin acetyltransferase and serotonin acetylase; $IC_{50} = 150$ nM). A synthetic bisubstrate compound incorporating the indole and coenzyme A moieties of the two substrates (tryptamine and acetyl-CoA), it is potentially useful as a tool for elucidating the biological functions of melatonin and pineal serotonin, and possibly also as a therapeutic agent.

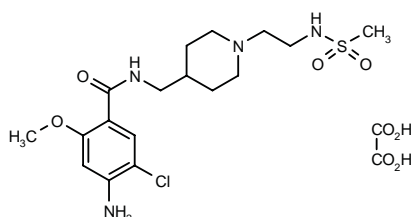
The enzyme catalyzes the conversion of serotonin to *N*-acetylserotonin, which is the immediate precursor of melatonin, in the pineal gland.

SOURCE – Rockefeller University, New York, NY (US).

REFERENCES

1. Cole, P.A. and Khalil, E. (Rockefeller University) *Inhibitors of serotonin N-acetyltransferase.* US 5990094.

280685

4-Amino-5-chloro-2-methoxy-*N*-[1-[2-(methylsulfonamido)ethyl]piperidin-4-ylmethyl]benzamide oxalate

C17 H27 Cl N4 O4 S . C2 H2 O4; Mol wt: 508.9771

M.p. 177-8 °C (decomp.).

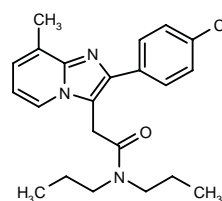
ACTION – Potent and selective 5-HT₄ receptor agonist ($ED_{50} = 7.0$ nM in guinea pig ascending colon) with nanomolar affinity for the 5-HT₄ receptor ($K_i = 9.6$ nM for displacement of [³H]-GR-113808 binding from guinea pig striatum) and high selectivity over a series of receptors including 5-HT_{1A}, 5-HT₂, 5-HT₃ and dopamine D₂ receptors and α_1 -adrenoceptors ($K_i > 1000$ nM). Potentially useful as a pharmacological tool for studying 5-HT₄ receptor function *in vivo*.

SOURCE – Yoshitomi (Welfide).

REFERENCES

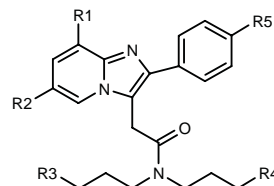
1. Itoh, K. et al. *Synthesis and pharmacological evaluation of carboxamide derivatives as selective serotoninergic 5-HT₄ receptor agonists.* Eur J Med Chem 1999, 34(11): 977.

280782

2-[2-(4-Chlorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl]-*N,N*-dipropylacetamide

C22 H26 Cl N3 O; Mol wt: 383.9204

ACTION – High-affinity ligand for the peripheral benzodiazepine site on the GABA_A receptor complex ($pIC_{50} = 8.85$ and 8.55 for cortex and ovarian receptors, respectively) with high selectivity over the central benzodiazepine receptor site ($pIC_{50} = 2.4$). *In vivo*, at a dose of 25 mg/kg i.p., it significantly increased both plasma and brain concentrations of neuroactive steroids including pregnenolone, progesterone, allopregnanolone and allotetrahydrodeoxycorticosterone by 126, 103, 85 and 83%, respectively, in plasma and 87, 101, 73 and 50%, respectively, in cerebral cortex. Potentially useful as a pharmacological tool for understanding the pharmacology and physiology of peripheral benzodiazepine receptor sites. Other 2-phenylimidazo[1,2-a]pyridine derivatives include the following:



Compound	R1	R2	R3=R4	R5	Formula
280781	H	CO ₂ Me	H	H	C ₂₃ H ₂₇ N ₃ O ₃
280783	Cl	H	H	Cl	C ₂₁ H ₂₃ Cl ₂ N ₃ O
280784	H	H	Me	H	C ₂₃ H ₂₉ N ₃ O

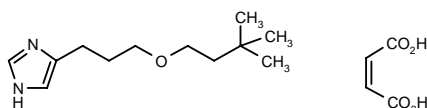
SOURCES – Università di Bari, Bari (IT); Università degli Studi di Cagliari, Cagliari (IT).

REFERENCES

1. Trapani, G. et al. *Novel 2-phenylimidazo[1,2-a]pyridine derivatives as potent and selective ligands for peripheral benzodiazepine receptors: Synthesis, binding affinity, and in vivo studies.* J Med Chem 1999, 42(19): 3934.

281395

4-[3-(3,3-Dimethylbutoxy)propyl]-1*H*-imidazole maleate



C₁₂H₂₂N₂O . C₄H₄O₄; Mol wt: 326.3904

M.p. 91 °C.

ACTION – Histamine H₃ receptor partial agonist (pK_i = 7.85 in rat cerebral cortical synaptosomes; pK_B = 7.03 in guinea pig ileum) with high selectivity over H₁ and H₂ receptors (pK_B = 3.5 and 4.5 in guinea pig atrium and ileum, respectively). Compound exhibited full agonist activity *in vivo*, as demonstrated by decrease in *N*-methylhistamine levels in cerebral cortex after oral dosing in mice (ED₅₀ = 0.29 mg/kg p.o.).

SOURCES – Bioprojet; INSERM, Paris Cedex (FR).

REFERENCES

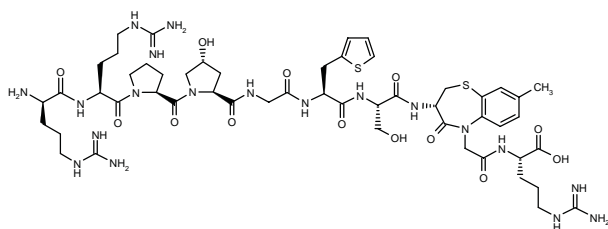
1. Schwartz, J.-C. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale]; Societe Civile Bioprojet) *Imidazole derivs. as histamine receptor H3 (ant)agonists*. EP 760811, FR 2732017, JP 98501001, WO 9629315.

2. Sasse, A. et al. *Novel partial agonists for the histamine H3 receptor with high in vitro and in vivo activity*. J Med Chem 1999, 42(20): 4269.

JMV-1609^{*,1,3}

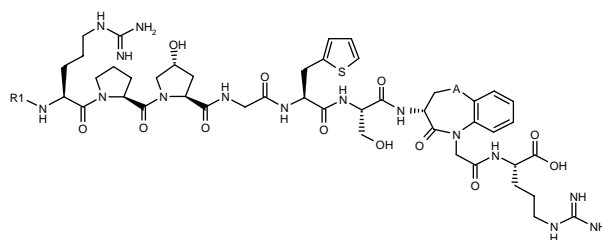
267534

N-[2-[3(*S*)-[D-Arginyl-L-arginyl-L-prolyl-L-[4(*R*)-hydroxy]prolyl-glycyl-L-(2-thienyl)alanyl-L-serylaminol]-8-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-5-yl]acetyl-L-arginine



C₅₂H₇₉N₁₉O₁₃S₂; Mol wt: 1242.4480

ACTION – Dipeptide-mimetic bradykinin analogue with high affinity and selectivity for the human bradykinin B₂ receptor (K_i = 6 nM) over the B₁ receptor (K_i > 100 μM) and full agonist activity in inducing contractions in human umbilical vein (pD₂ = 7.4), where it was as effective as bradykinin itself (pD₂ = 7.9). Compound is apparently resistant to enzymatic cleavage by endopeptidases and may thus be a useful pharmacological tool. Other related compounds include the following:



Compound	R1	A	Formula
JMV-1645 [266233] ^{*,1,3}	H-L-Lys-	S	C ₅₁ H ₇₇ N ₁₇ O ₁₃ S ₂
JMV-1116 [267531] ^{*,1,3}	H-D-Arg-	S	C ₅₁ H ₇₇ N ₁₉ O ₁₃ S ₂
JMV-1442 [267533] ^{*,1,3}	H-D-Arg-	O	C ₅₁ H ₇₇ N ₁₉ O ₁₄ S

SOURCE – Fournier.

REFERENCES

1. Dodey, P. et al. (Fournier Industrie et Santé) *Peptides agonists of bradykinin B2 receptor*. FR 2756566, WO 9824809.

2. Amblard, M. et al. *Design and synthesis of potent bradykinin agonists containing a benzothiazepine moiety*. J Med Chem 1999, 42(20): 4185.

3. Amblard, M. et al. *Synthesis and characterization of bradykinin B2 receptor agonists containing constrained dipeptide mimics*. J Med Chem 1999, 42(20): 4193.

*Identified compound **267534** (see **266233**) Drug Data Rep 1998, 020(09): 0771.

Identified compound **266233 Drug Data Rep 1998, 020(09): 0771.

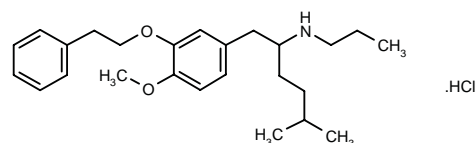
***Identified compound **267531** (see **266233**) Drug Data Rep 1998, 020(09): 0771.

****Identified compound **267533** (see **266233**) Drug Data Rep 1998, 020(09): 0771.

NE-535^{*}

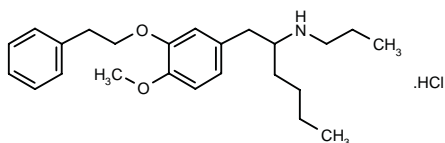
247610

(-)-*N*-[1-[4-Methoxy-3-(2-phenylethoxy)benzyl]-4-methylpentyl]-*N*-propylamine hydrochloride



C₂₅H₃₇N O₂ . HCl; Mol wt: 420.0332

ACTION – Potent and selective σ₁-receptor ligand (IC₅₀ = 0.5 nM) with high selectivity over σ₂- and dopamine D₂ receptors (IC₅₀ = 200 and > 1000 nM, respectively). Potentially useful as a pharmacological tool for examining the physiological and clinical significance of this receptor subtype. Another representative 1-alkyl-2-phenylethylamine is:



NE-537 [248047]:** C₂₄ H₃₅ N O₂ . HCl

SOURCE – Taisho.

REFERENCES

1. Nakazato, A. et al. (Taisho Pharmaceutical Co., Ltd.) *Optically active subst. phenylalkylamine derivs.* EP 870758, JP 97059230, US 5990151, WO 9700238.

2. Nakazato, A. et al. *Synthesis and SAR of 1-alkyl-2-phenylethylamine derivatives designed from N,N-dipropyl-4-methoxy-3-(2-phenylethoxy)phenylethylamine to discover sigma1 ligands.* J Med Chem 1999, 42(19): 3965.

*Identified compound **247610** Drug Data Rep 1997, 019(05): 0398.

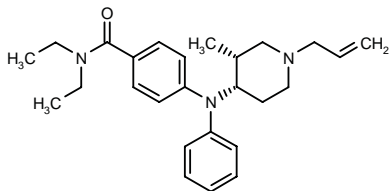
Identified compound **248047 (see **247610**) Drug Data Rep 1997, 019(05): 0398.

ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

282070

cis-4-[*N*-(1-Allyl-3-methylpiperidin-4-yl)-*N*-phenylamino]-*N,N*-diethylbenzamide



C26 H35 N3 O; Mol wt: 405.5825

ACTION – δ -Opioid receptor agonist (K_i = 11.9 nM) with high selectivity over μ - and κ -opioid receptors (K_i = 1212 and 3284 nM, respectively); it is able to stimulate [35 S]-GTP γ S binding (K_d = 3.5 μ M) in the presence of the μ - and κ -selective opioid antagonists NTI and CTAP, but not the δ -selective antagonist naltrindole. Such compounds may have potential as analgesics with reduced side effects relative to morphine.

SOURCES – Ortho-McNeil; Research Triangle Institute, Research Triangle Park, NC (US).

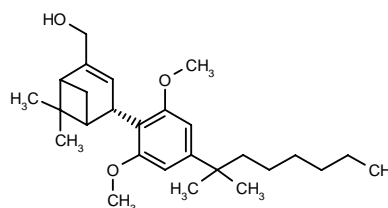
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2. Carson, J.R. et al. (Ortho-McNeil Pharmaceutical, Inc.) 4-[Aryl(piperidin-4-yl)] aminobenzamides which bind to the δ -opioid receptor. WO 9933806.
3. Thomas, J.B. et al. (\pm)-4-[(*N*-Allyl-*cis*-3-methyl-4-piperidinyl)phenylamino]-*N,N*-diethylbenzamide displays selective binding for the δ opioid receptor. *Bioorg Med Chem Lett* 1999, 9(20): 3053.

HU-308

283321

1-[4(*R*)-[4-(1,1-Dimethylheptyl)-2,6-dimethoxyphenyl]-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]methanol



C27 H42 O3; Mol wt: 414.6258

ACTION – High-affinity cannabinoid CB₂ receptor ligand (K_i = 22.7 nM) with high selectivity over CB₁ receptors (K_i > 10 μ M); CB₂-agonist activity was demonstrated by its ability to inhibit forskolin-stimulated cAMP production (EC_{50} = 5.57 nM) in CB₂-transfected CHO cells. Compound displayed much less activity in CB₁-transfected cells (about 10% inhibition at 1 μ M, 72% inhibition at 10 μ M) and had no effect in cells not transfected with cannabinoid receptors. Compound reduced blood pressure (at 30 mg/kg i.v.) in anesthetized rats, inhibited defecation in mice (at 20 mg/kg i.p.) and evoked antiinflammatory and peripheral analgesic effects in murine models (at 50 mg/kg i.p.); these effects were at least partially blocked by the CB₂ antagonist SR-144528, but not by the CB₁ antagonist SR-141716A. It demonstrated a lack of CB₁ receptor-mediated behavioral effects in mice such as reduction in motor activity in an open field, induction of catalepsy or analgesia and reduction in body temperature. A potential nonpsychotropic therapy for hypertension, inflammation and pain.

SOURCES – University of Aberdeen, Aberdeen (GB); Hebrew University, Jerusalem (IL).

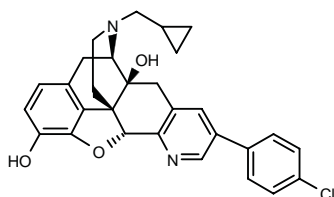
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1. Hanus, L. et al. HU-308: A specific agonist for CB₂, a peripheral cannabinoid receptor. *Proc Natl Acad Sci USA* 1999, 96(25): 14228.

SoRI-9409

280338

5'-(4-Chlorophenyl)-17-(cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5 α -epoxy-pyrido[2',3':6,7]morphinan



C29 H27 Cl N2 O3; Mol wt: 486.9963

M.p > 175 °C.

ACTION – Opioid analgesic, a nonpeptide ligand with high affinity for δ -receptors ($K_i = 2.2$ nM) relative to μ - and κ -receptors ($K_i = 51$ and 20 nM, respectively). High functional δ -antagonist activity was seen in mouse vas deferens ($K_o = 0.66$ nM) and moderate μ -agonist activity was observed in guinea pig ileum ($IC_{50} = 163$ nM). In antinociceptive studies in mice, compound administered by intracerebroventricular (i.c.v.) injection exhibited partial agonist activity in the tail-flick test ($A_{50} > 100$ nmol), whereas it displayed full agonist activity in the acetic acid-induced writhing assay ($A_{50} = 7.5$ nmol); repeated i.c.v. injections of compound at an A_{90} dose were not associated with the development of tolerance in the writhing assay, in contrast to morphine.

SOURCE – Southern Research Institute, Birmingham, AL (US).

REFERENCES

1. Ananthan, S. et al. *Synthesis, opioid receptor binding, and biological activities of naltrexone-derived pyrido- and pyrimidomorphinans*. J Med Chem 1999, 42(18): 3527.
2. Matthews, J.L. et al. *Characterization of the antinociceptive actions of SoRI 9409, an opioid μ agonist/ δ antagonist*. Soc Neurosci Abst 1999, 25(Part 1): Abst 375.5.

SUBSTANCE P-SAPORIN

282649

Conjugate of substance P and the ribosome-inactivating protein saporin (SAP)

SP-SAP

Substance P-SAP

ACTION – Analgesic agent for the treatment of chronic neuropathic and inflammatory pain, a conjugate of substance P and the ribosome-inactivating protein saporin (SAP) proven to produce a loss of lamina I spinal cord neurons expressing substance P receptors 30 days after administration into the dorsal horn of the spinal cord in rats. This treatment attenuated thermal and mechanical hyperalgesia and mechanical allodynia produced by capsaicin, nerve injury or inflammation; it did not affect morphine analgesia or formalin-induced pain and there was no evidence of loss of effect over time.

SOURCES – University of Minnesota, Minneapolis, MN (US); Veterans Affairs Medical Center, Minneapolis, MN (US).

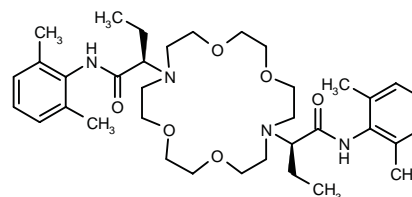
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2. Honore, P. et al. *Spinal injection of substance P-saporin toxin is cytotoxic to lamina I neurons that express the substance P receptor and profoundly attenuates thermal and mechanical hyperalgesia*. Soc Neurosci Abst 1997, 23(Part 2): Abst 702.12.
3. Nichols, M.L. et al. *Long term antihyperalgesic effects of the substance P-saporin toxin and suppression of chronic pain*. Soc Neurosci Abst 1998, 24(Part 2): Abst 547.12.
4. Nichols, M.L. et al. *Transmission of chronic nociception by spinal neurons expressing the substance P receptor*. Science 1999, 286(5444): 1558.
5. Rogers, S.D. et al. *Internalization and cytotoxicity of a substance P-saporin chemical conjugate in spinal cord neurons in vitro and in vivo: Using ligand induced receptor endocytosis as a specific portal of entry into cells*. Soc Neurosci Abst 1997, 23(Part 2): Abst 702.13.
6. Wiley, R.G. and Lappi, D.A. *Destruction of neurokinin-1 receptor expressing cells in vitro and in vivo using substance P-saporin in rats*. Neurosci Lett 1997, 230(2): 97.
7. Wiley, R.G. and Lappi, D.A. *SSP-SAP, an improved neurotoxin selective for neurons expressing the neurokinin-1 receptor: Anatomic and pain perception effects of striatal*. Soc Neurosci Abst 1997, 23(Part 2): Abst 702.16.

ANESTHETIC DRUGS

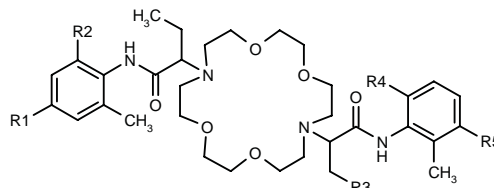
282140

2(R),2'(R)-(1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis[N-(2,6-dimethylphenyl)butyramide]



C36 H56 N4 O6; Mol wt: 640.8604

ACTION – Local anesthetic agent that binds to multiple sites on voltage-gated Na⁺ ion channels and which is reported to produce local anesthesia of longer duration than the corresponding unlinked monovalent ligands and to have greatly reduced or negligible systemic toxicity compared to monovalent anesthetics. Other exemplified multibinding compounds include the following:



Compound	R1	R2	R3	R4	R5	Formula
282142	H	Me	Me	Me	H	C ₃₆ H ₅₆ N ₄ O ₆
282143	CH ₂ CH ₂ -CO ₂ Me	Me	Me	H	H	C ₃₉ H ₆₀ N ₄ O ₈
282144	H	Me	Me	H	OCH ₂ -CO ₂ Et	C ₃₉ H ₆₀ N ₄ O ₉
282146	H	CH=CH-CO ₂ Me	H	H	H	C ₃₇ H ₅₄ N ₄ O ₈

SOURCE – Advanced Medicine.

REFERENCES

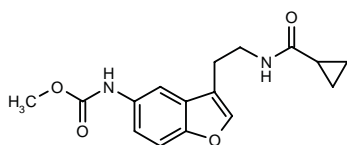
1. Axt, S.M. et al. (Advanced Medicine, Inc.) *Novel local anesthetic cpds. and uses*. WO 9951565.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

283669

N-[3-[2-(Cyclopropylcarboxamido)ethyl]benzofuran-5-yl]carbamic acid methyl ester



C₁₆ H₁₈ N₂ O₄; Mol wt: 302.3282

ACTION – Agent with strong affinity for melatonin receptors, potentially useful for the treatment of a broad range of disorders including seasonal depression, sleep disorders, cardiovascular disorders, insomnia and fatigue due to time changes, appetite disorders and obesity. It is reported to exert anxiolytic activity and to have a potent effect on circadian rhythms via the melatonergic system in animal models.

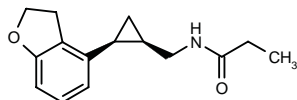
SOURCE – ADIR.

REFERENCES

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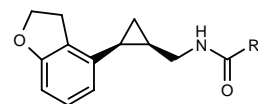
284017

cis-*N*-[2-(2,3-Dihydrobenzofuran-4-yl)cyclopropylmethyl]propionamide



C₁₅ H₁₉ N O₂; Mol wt: 245.3201

ACTION – Melatonergic agent that binds to the human melatonin MEL_{1A} (mt₁) receptor (IC₅₀ < 50 nM) and demonstrates agonist activity by its ability to block the forskolin-stimulated accumulation of cAMP in cells. Potentially useful in the treatment of stress, sleep disorders, seasonal depression, appetite disorders, shifts in circadian rhythms, benign prostatic hyperplasia, inflammatory articular disease and headache. Other exemplified heterocyclic *cis*-cyclopropane derivatives are:



Compound	R1	Formula
284018	Me	C ₁₄ H ₁₇ NO ₂
284020	cyclopropyl	C ₁₆ H ₁₉ NO ₂
284021	Pr	C ₁₆ H ₂₁ NO ₂
284022	i-Pr	C ₁₆ H ₂₁ NO ₂

SOURCE – Bristol-Myers Squibb.

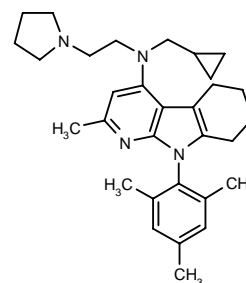
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ANXIOLYTICS

281928

N-(Cyclopropylmethyl)-*N*-[2-methyl-9-(2,4,6-trimethylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-4-yl]-*N*-[2-(1-pyrrolidinyl)ethyl]amine



C₃₁ H₄₂ N₄; Mol wt: 470.7008

ACTION – A corticotropin-releasing factor CRF₁ receptor antagonist with potential in the treatment of stress-related disorders, anxiety, depression, headache, irritable bowel syndrome, supranuclear palsy, Alzheimer's disease, eating disorders, drug addiction, inflammation, cardiovascular diseases, HIV infection and hypoglycemia. Other specifically claimed compounds within this series of aminoalkyl-substituted 5,6,7,8-tetrahydro-9*H*-pyrido[2,3-*b*]indole and 5,6,7,8-tetrahydro-9*H*-pyrimido[4,5-*b*]indole derivatives include the following:

SOURCE – Advanced Medicine.

REFERENCES

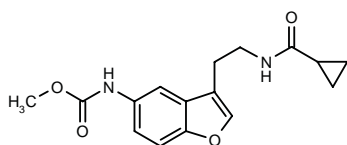
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PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

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N-[3-[2-(Cyclopropylcarboxamido)ethyl]benzofuran-5-yl]carbamic acid methyl ester



C₁₆ H₁₈ N₂ O₄; Mol wt: 302.3282

ACTION – Agent with strong affinity for melatonin receptors, potentially useful for the treatment of a broad range of disorders including seasonal depression, sleep disorders, cardiovascular disorders, insomnia and fatigue due to time changes, appetite disorders and obesity. It is reported to exert anxiolytic activity and to have a potent effect on circadian rhythms via the melatonergic system in animal models.

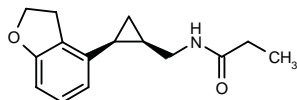
SOURCE – ADIR.

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1. Lesieur, D. et al. (ADIR et Cie.) *Novel subst. cyclic cpds., preparation method and pharmaceutical compsns. containing them*. FR 2778662, WO 9958495, WO 9958496.

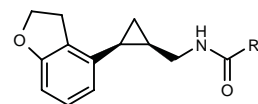
284017

cis-*N*-[2-(2,3-Dihydrobenzofuran-4-yl)cyclopropylmethyl]propionamide



C₁₅ H₁₉ N O₂; Mol wt: 245.3201

ACTION – Melatonergic agent that binds to the human melatonin MEL_{1A} (mt₁) receptor (IC₅₀ < 50 nM) and demonstrates agonist activity by its ability to block the forskolin-stimulated accumulation of cAMP in cells. Potentially useful in the treatment of stress, sleep disorders, seasonal depression, appetite disorders, shifts in circadian rhythms, benign prostatic hyperplasia, inflammatory articular disease and headache. Other exemplified heterocyclic *cis*-cyclopropane derivatives are:



Compound	R1	Formula
284018	Me	C ₁₄ H ₁₇ NO ₂
284020	cyclopropyl	C ₁₆ H ₁₉ NO ₂
284021	Pr	C ₁₆ H ₂₁ NO ₂
284022	i-Pr	C ₁₆ H ₂₁ NO ₂

SOURCE – Bristol-Myers Squibb.

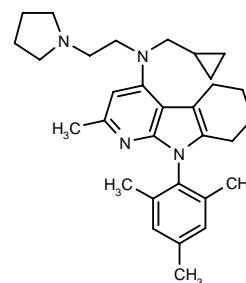
REFERENCES

1. Chen, J. et al. (Bristol-Myers Squibb Co.) *Heterocyclic cis cyclopropane derivs. as melatonergic agents*. WO 9962515.

ANXIOLYTICS

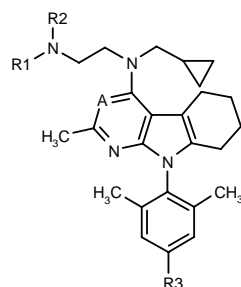
281928

N-(Cyclopropylmethyl)-*N*-[2-methyl-9-(2,4,6-trimethylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-4-yl]-*N*-[2-(1-pyrrolidinyl)ethyl]amine



C₃₁ H₄₂ N₄; Mol wt: 470.7008

ACTION – A corticotropin-releasing factor CRF₁ receptor antagonist with potential in the treatment of stress-related disorders, anxiety, depression, headache, irritable bowel syndrome, supranuclear palsy, Alzheimer's disease, eating disorders, drug addiction, inflammation, cardiovascular diseases, HIV infection and hypoglycemia. Other specifically claimed compounds within this series of aminoalkyl-substituted 5,6,7,8-tetrahydro-9*H*-pyrido[2,3-*b*]indole and 5,6,7,8-tetrahydro-9*H*-pyrimido[4,5-*b*]indole derivatives include the following:



Compound	R1	R2	R3	A	Formula
281929	Me	Me	Me	CH	C ₂₉ H ₄₀ N ₄
281930	Me	Me	Me	N	C ₂₈ H ₃₉ N ₅
281931	CH ₂ CH ₂ OMe	H	Me	CH	C ₃₀ H ₄₂ N ₄ O
281932	H	H	H	CH	C ₂₆ H ₃₄ N ₄

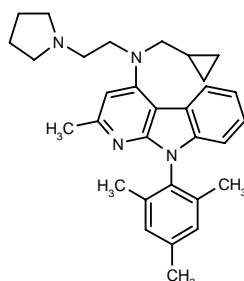
SOURCE – Neurogen.

REFERENCES

1. Horvath, R.F. et al. (Neurogen Corp.) *Aminoalkyl subst. 5,6,7,8-tetrahydro-9H-pyrimidino[2,3-b]indole and 5,6,7,8-tetrahydro-9H-pyrimidino[4,5-b]indole derivs: CRF1 specific ligands.* WO 9951597.

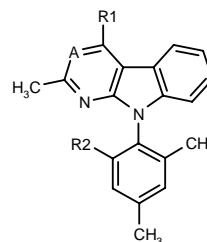
281947

N-(Cyclopropylmethyl)-*N*-[2-methyl-9-(2,4,6-trimethylphenyl)-9*H*-pyrido[2,3-*b*]indol-4-yl]-*N*-[2-(1-pyrrolidinyl)ethyl]amine



C31 H38 N4; Mol wt: 466.6692

ACTION – Agent for the treatment of depression, headache, anxiety, posttraumatic stress disorder, supranuclear palsy, as well as immunological, cardiovascular and eating disorders, diabetes and stress, a dual corticotropin-releasing factor CRF₁ receptor antagonist and neuropeptide Y (NPY) Y₁ receptor antagonist. Other specifically claimed compounds within this series of aminoalkyl-substituted 9*H*-pyrido[2,3-*b*]indole and 9*H*-pyrimido[4,5-*b*]indole derivatives include the following:



Compound	R1	R2	A	Formula
281948	1-Pip-CH ₂ CH ₂ N(CH ₂ -cyclopropyl)	Me	CH	C ₃₂ H ₄₀ N ₄
281949	1-pyrrolidinyl-CH ₂ CH ₂ -N(CH ₂ -cyclopropyl)	H	CH	C ₃₀ H ₃₆ N ₄
281950	N(<i>i</i> -Bu)CH ₂ CH ₂ N(Me) ₂	Me	CH	C ₂₉ H ₃₈ N ₄
281951	N(CH ₂ -cyclopropyl)(CH ₂) ₃ NH ₂	Me	CH	C ₂₈ H ₃₄ N ₄
281952	N(CH ₂ -cyclopropyl)-CH ₂ CH ₂ N(Me)SO ₂ Me	Me	CH	C ₂₉ H ₃₆ N ₄ O ₂ S
281953	N(CH ₂ -cyclopropyl)COCH ₂ NHEt	Me	CH	C ₂₉ H ₃₄ N ₄ O
281954	1-Me-2-pyrrolidinyl-CH ₂ CH ₂ N(CH ₂ -cyclopropyl)	Me	CH	C ₃₂ H ₄₀ N ₄
281955	N(Me)CH ₂ CH ₂ N(Me) ₂	Me	N	C ₂₅ H ₃₁ N ₅
281956	3-NH ₂ -1,2,4-triazol-1-yl	Me	N	C ₂₂ H ₂₁ N ₇
281957	N(cyclobutyl)CH ₂ CH ₂ N(Me) ₂	Me	N	C ₂₈ H ₃₅ N ₅
281958	N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ N(Me) ₂	Me	N	C ₂₇ H ₃₅ N ₅ O

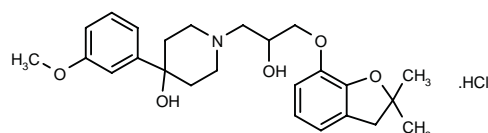
SOURCE – Neurogen.

REFERENCES

1. Horvath, R.F. et al. (Neurogen Corp.) *Aminoalkyl subst. 9H-pyrido[2,3-b]indole and 9H-pyrimido[4,5-b]indole derivs.* WO 9951600.

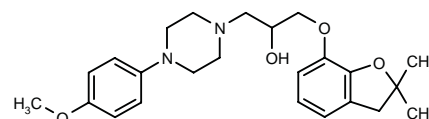
284146

1-[3-(2,2-Dimethyl-2,3-dihydrobenzofuran-7-yloxy)-2-hydroxypropyl]-4-(3-methoxyphenyl)-4-piperidinol hydrochloride



C25 H33 N O5 . HCl; Mol wt: 463.9986

ACTION – Agent for the treatment of CNS disorders with high affinity for the 5-HT_{1A} receptor (K_i = 0.7 nM against [³H]-8-OH-DPAT binding in rat frontal cortex membranes). Anxiolytic activity was demonstrated *in vivo* in the elevated plus-maze test in rats, where it exhibited a minimum effective dose (MED) of 0.3 mg/kg p.o., being 10-fold more potent than buspirone (MED = 3 mg/kg p.o.). Another compound from this broad series of benzofuran derivatives is:



283670: C24 H32 N2 O4

Other compounds within the scope of the patent are reported to exhibit cardioprotective effects*.

SOURCE – Egis.

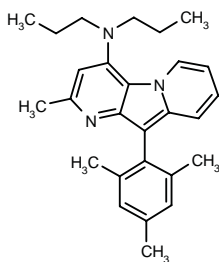
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1. Ágal, B. et al. (Egis Pharmaceuticals Ltd.) *Benzofuran derivs., pharmaceutical compns. containing the same, and a process for the preparation of the active ingredient.* WO 9958527.

*See **284145** under TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS.

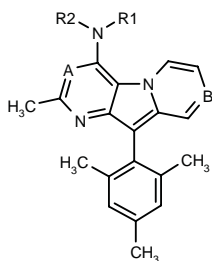
284511

N-[2-Methyl-10-(2,4,6-trimethylphenyl)pyrido[2,3-*b*]-indolizin-4-yl]-*N,N*-dipropylamine



C27 H33 N3; Mol wt: 399.5787

ACTION – Agent for the treatment of stress-related disorders such as posttraumatic stress disorder (PTSD), as well as depression, headache and anxiety, a representative compound from a series of pyrido[2,3-*b*]-indolizine derivatives and aza analogues with partial agonist or antagonist activity at human corticotropin-releasing factor (CRF) receptors, wherein the following are also specifically claimed:



Compound	R1	R2	A	B	Formula
284512	Pr	cyclopropyl-CH ₂	CH	CH	C ₂₈ H ₃₃ N ₃
284513		-CH ₂ CH ₂ OCH ₂ CH ₂ -	CH	CH	C ₂₅ H ₂₇ N ₃ O
284514	CH ₂ CH ₂ OMe	CH ₂ CH ₂ OMe	CH	CH	C ₂₇ H ₃₃ N ₃ O ₂
284515	Et	CH ₂ Ph	N	CH	C ₂₉ H ₃₀ N ₄
284516	Pr	cyclopropyl-CH ₂	N	CH	C ₂₇ H ₃₂ N ₄
284517	CH ₂ CH ₂ OMe	CH ₂ CH ₂ OMe	N	CH	C ₂₈ H ₃₂ N ₄ O ₂
284518	Pr	Pr	CH	N	C ₂₆ H ₃₂ N ₄
284519		-CH ₂ CH ₂ OCH ₂ CH ₂ -	CH	N	C ₂₄ H ₂₆ N ₄ O
284520	CH ₂ CH ₂ OMe	CH ₂ CH ₂ OMe	CH	N	C ₂₆ H ₃₂ N ₄ O ₂

SOURCE – Neurogen.

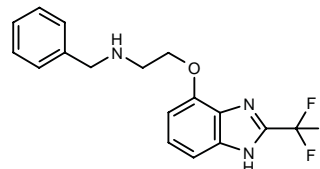
REFERENCES

1. Yoon, T. (Neurogen Corp.) *Pyrido[2,3-*b*]indolizine derivs. and aza analogues thereof: CRF1 specific ligands.* WO 9964422.

ANTIPSYCHOTIC DRUGS

280673

4-[2-(Benzylamino)ethoxy]-2-trifluoromethyl-1*H*-benzimidazole



C17 H16 F3 N3 O; Mol wt: 335.3274

ACTION – Potential antipsychotic agent, a dopamine D₂ receptor partial agonist with subnanomolar affinity for rat striatal D₂ receptors (K_i = 0.18 nM) and nanomolar affinity for human D₂, D₃ and D_{4.4} receptors (K_i = 1.75, 1.15 and 3.1 nM, respectively). In mice, compound exhibited a D₂ partial agonist profile, as demonstrated by reduction in spontaneous motility (ED₅₀ = 0.007 µg/kg s.c.) and by inhibition of apomorphine-induced climbing and stereotypy (ED₅₀ = 0.09 and 0.33 mg/kg s.c., respectively).

SOURCE – American Home Products.

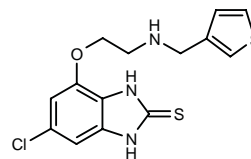
REFERENCES

1. Nelson, J.A. and Mewshaw, R.E. (American Home Products Corp.) *4-Aminoalkoxy-1H-benzimidazole derivs., their preparation and their use as dopamine autoreceptor (D2) agonists.* EP 973749, WO 9835945.

2. Mewshaw, R.E. et al. *New generation dopaminergic agents 7. Heterocyclic bioisosteres that exploit the 3-OH-phenoxyethylamine D2 template.* Bioorg Med Chem Lett 1999, 9(17): 2593.

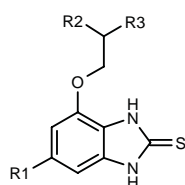
282222¹

6-Chloro-4-[2-(3-thienylmethylamino)ethoxy]-2,3-dihydro-1*H*-benzimidazole-2-thione



C14 H14 Cl N3 O S₂; Mol wt: 339.8696

ACTION – Antipsychotic agent free of extrapyramidal side effects that acts as a dopamine autoreceptor agonist and thus selectively activates autoreceptors versus post-synaptic dopamine D₂ receptors, as demonstrated in a binding assay by an IC₅₀ value of 0.18 nM against [³H]-quinpirole binding in rat striatal brain tissue as compared to an IC₅₀ of 85.0 nM against [³H]-spiperidol binding in homogenized limbic brain tissue (ratio IC₅₀s = 472.2). Within this series of 4-aminoalkoxy-1,3-dihydrobenzimidazole-2-thione derivatives, the following are also included:



Compound	R1	R2	R3	Formula
282223 ^{1,2}	H	H	NHCH ₂ Ph	C ₁₆ H ₁₇ N ₃ OS
282224 ¹	H	H	4-Me-PhCH ₂ NH	C ₁₇ H ₁₉ N ₃ OS
282225 ¹	H	Me	NHCH ₂ Ph	C ₁₇ H ₁₉ N ₃ OS
282226 ¹	H	H	1-Naph-CH ₂ NH	C ₂₀ H ₁₉ N ₃ OS
282227 ¹	H	H	4-t-Bu-PhCH ₂ NH	C ₂₀ H ₂₅ N ₃ OS
282228 ¹	H	H	4-Cl-PhCH ₂ NH	C ₁₆ H ₁₆ ClN ₃ OS
282229 ^{1,2}	Cl	H	NHCH ₂ Ph	C ₁₆ H ₁₆ ClN ₃ OS
282230 ¹	Cl	H	2-thienyl-CH ₂ NH	C ₁₄ H ₁₄ ClN ₃ OS ₂
282231 ¹	H	H	1,2,3,4-tetrahydro-2-isoquinoliny	C ₁₈ H ₁₉ N ₃ OS

SOURCE – American Home Products.

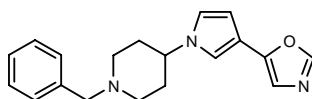
REFERENCES

1. Nelson, J.A. et al. (American Home Products Corp.) 4-Aminoalkoxy-1,3-dihydrobenzimidazol-2-thiones. US 5972958.

2. Mewshaw, R.E. et al. New generation dopaminergic agents 7. Heterocyclic bioisosteres that exploit the 3-OH-phenoxyethylamine D2 template. Bioorg Med Chem Lett 1999, 9(17): 2593.

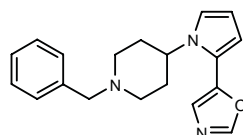
282759

1-Benzyl-4-[3-(5-oxazolyl)-1H-pyrrol-1-yl]piperidine



C₁₉ H₂₁ N₃ O; Mol wt: 307.3949

ACTION – High-affinity dopamine D_{4.4} receptor ligand (K_i = 130 nM) with high selectivity over dopamine D₁, D_{2L}, D_{2S} and D₃ receptors (K_i = 39, 3.4, 3.2 and 6.8 μM, respectively); compared to clozapine, compound showed 8-fold lower affinity for the human D_{4.4} receptor but significantly higher selectivity over other dopamine receptor subtypes. Potentially useful as an atypical antipsychotic agent. Another related compound is:



282760: C₁₉ H₂₁ N₃ O

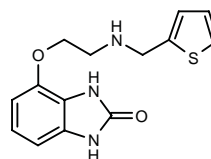
SOURCE – Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen (DE).

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1. Haubmann, C. et al. Piperidinylopyrroles: Design, synthesis and binding properties of novel and selective dopamine D₄ receptor ligands. Bioorg Med Chem Lett 1999, 9(21): 3143.

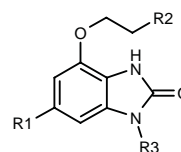
283331¹

4-[2-(2-Thienylmethylamino)ethoxy]-2,3-dihydro-1H-benzimidazol-2-one



C₁₄ H₁₅ N₃ O₂ S; Mol wt: 289.3575

ACTION – A selective dopamine autoreceptor agonist, as demonstrated in a binding assay in rat striatal brain tissue using [³H]-quinpirole as the ligand (IC₅₀ = 0.51 nM), with much lower affinity for postsynaptic dopamine D₂ receptors (IC₅₀ = 254.6 nM against [³H]-spiroperidol binding in limbic brain tissue). Potentially useful for the treatment of schizophrenia, Parkinson's disease, Tourette's syndrome and alcohol or drug addiction. Other specifically claimed compounds from this series of 4-aminoalkoxy-1,3-dihydrobenzimidazol-2-one derivatives include the following:



Compound	R1	R2	R3	Formula
283332 ^{1,2}	H	NHCH ₂ Ph	H	C ₁₆ H ₁₇ N ₃ O ₂
283333 ¹	H	4-Me-PhCH ₂ NH	H	C ₁₇ H ₁₉ N ₃ O ₂
283334 ¹	H	NHCH ₂ Ph	Me	C ₁₇ H ₁₉ N ₃ O ₂
283335 ¹	H	CH ₂ NHCH ₂ Ph	H	C ₁₇ H ₁₉ N ₃ O ₂
283336 ¹	H	1-Naph-CH ₂ NH	H	C ₂₀ H ₁₉ N ₃ O ₂
283337 ¹	H	4-t-Bu-PhCH ₂ NH	H	C ₂₀ H ₂₅ N ₃ O ₂
283338 ¹	H	4-Cl-PhCH ₂ NH	H	C ₁₆ H ₁₆ ClN ₃ O ₂
283339 ^{1,2}	Cl	NHCH ₂ Ph	H	C ₁₆ H ₁₆ ClN ₃ O ₂
283340 ¹	Cl	2-thienyl-CH ₂ NH	H	C ₁₄ H ₁₄ ClN ₃ O ₂ S
283341 ¹	Cl	3-thienyl-CH ₂ NH	H	C ₁₄ H ₁₄ ClN ₃ O ₂ S

SOURCE – American Home Products.

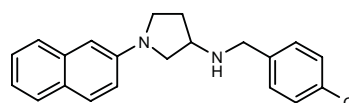
REFERENCES

1. Mewshaw, R.E. et al. (American Home Products Corp.) 4-Aminoalkoxy-1,3-dihydrobenzimidazol-2-one dopamine autoreceptor agonists. US 5990144.

2. Mewshaw, R.E. et al. New generation dopaminergic agents 7. Heterocyclic bioisosteres that exploit the 3-OH-phenoxyethylamine D2 template. Bioorg Med Chem Lett 1999, 9(17): 2593.

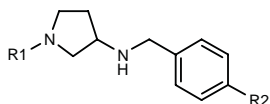
284396

N-(4-Chlorobenzyl)-N-[1-(2-naphthyl)pyrrolidin-3-yl]amine



C₂₁ H₂₁ Cl N₂; Mol wt: 336.8639

ACTION – Agent for the treatment of CNS disorders including schizophrenia, mania, depression, anxiety, dementia, Parkinson's disease, tardive dyskinesias, drug abuse, obsessive–compulsive disorder and motor disorders associated with the use of neuroleptic agents, a selective dopamine D₄ receptor antagonist (K_i = 209 nM vs. 1800 nM for D₂ receptors). Other specifically claimed compounds from this series of substituted 1-aryl-3-benzylaminopyrrolidine derivatives include the following:



Compound	R1	R2	Formula
284397	6-quinoxaliny	Cl	C ₁₉ H ₁₉ ClN ₄
284398	1,4-benzodioxan-6-yl	Cl	C ₁₉ H ₁₉ ClN ₂ O ₂
284400	2-quinoliny	Cl	C ₂₀ H ₂₀ ClN ₃
284401	2-Naph	Me	C ₂₂ H ₂₄ N ₂
284403	1,4-benzodioxan-6-yl	Me	C ₂₀ H ₂₂ N ₂ O ₂
284404	2-quinoliny	Me	C ₂₁ H ₂₃ N ₃

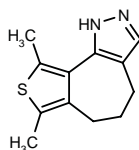
SOURCE – Neurogen.

REFERENCES

- Chen, X. and Wasley, J.W.F. (Neurogen Corp.) *Substd. 1-aryl-3-benzylamino-pyrrolidine: Dopamine receptor subtype specific ligands*. WO 9964396.

284510

7,9-Dimethyl-1,4,5,6-tetrahydrothieno[3',4':6,7]cyclohepta[1,2-*c*]pyrazole



C₁₂ H₁₄ N₂ S; Mol wt: 218.3226

ACTION – Agent for the treatment of CNS disorders including schizophrenia, mania, depression, anxiety, dementia, Parkinson's disease, tardive dyskinesias, drug abuse, obsessive–compulsive disorder and motor disorders associated with the use of neuroleptic agents, with high affinity and selectivity for dopamine D₄ receptors relative to D₂ receptors. A representative compound from a series of substituted thienocycloalkylpyrazole derivatives.

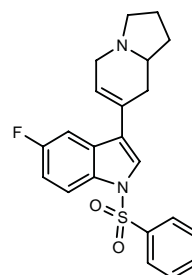
SOURCE – Neurogen.

REFERENCES

- Chen, X. and Wasley, J.W.F. (Neurogen Corp.) *Substd. thienocycloalkylpyrazoles: Dopamine receptor subtype specific ligands*. WO 9964425.

284612

5-Fluoro-3-(1,2,3,5,8,8a-hexahydroindolizin-7-yl)-1-(phenylsulfonyl)-1*H*-indole



C₂₂ H₂₁ F N₂ O₂ S; Mol wt: 396.4839

ACTION – Agent for the treatment or prevention of CNS disorders such as psychosis, schizophrenia, manic depression, depression, memory impairment, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease and Huntington's disease, a potent 5-HT₆ receptor antagonist (> 90% inhibition at 100 nM) with good selectivity relative to 5-HT_{2A}, 5-HT_{2C} and 5-HT₇ receptors (< 10% inhibition at 100 nM). A representative compound from a series of bicyclic piperidine and piperazine derivatives.

SOURCE – NPS Allelix.

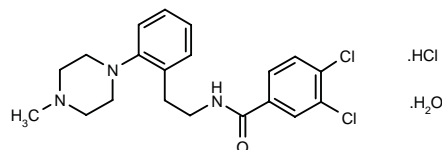
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- Maddaford, S. et al. (NPS Allelix Corp.) *Bicyclic piperidine and piperazine cpds. having 5-HT₆ receptor affinity*. WO 9965906.

TREATMENT FOR MOOD DISORDERS

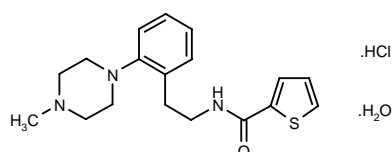
282118

3,4-Dichloro-*N*-[2-[2-(4-methyl-1-piperazinyl)phenyl]ethyl]benzamide hydrochloride hydrate



C₂₀ H₂₃ Cl₂ N₃ O . HCl . H₂O; Mol wt: 446.8034

ACTION – Agent for the treatment of depression, hypertension, generalized anxiety disorder, phobias, posttraumatic stress disorder, sexual dysfunction, eating disorders, chemical dependency, migraine, pain, Alzheimer's disease, obsessive–compulsive disorder, panic disorder, memory disorders, Parkinson's disease, vasospasm and gastrointestinal tract disorders with affinity for 5-HT_{1D} and 5-HT_{1A} receptors (IC₅₀ < 0.60 and < 1.0 μM, respectively). Another exemplified compound from this series of *N*-acyl and *N*-aroyl alkyl amides is:



282119: C₁₈ H₂₃ N₃ O S . HCl . H₂O

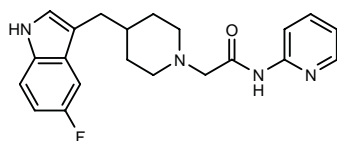
SOURCE – Pfizer.

REFERENCES

1. Howard, H.R. (Pfizer Products Inc.) *N-Acyl and N-aroyl aralkyl amides*. EP 952154.

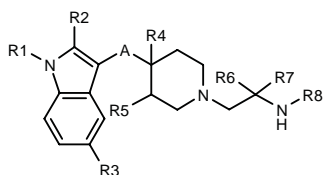
282580

2-[4-(5-Fluoro-1*H*-indol-3-ylmethyl)piperidin-1-yl]-*N*-(2-pyridyl)acetamide



C₂₁ H₂₃ F N₄ O; Mol wt: 366.4377

ACTION – Serotonergic agent shown to act as a 5-HT reuptake inhibitor ($K_i = 0.09$ nM for inhibition of [³H]-paroxetine binding in rat cortical membranes). Particularly useful in the treatment of depression, as well as anxiety, drug withdrawal, eating and sexual disorders, etc. Other specifically claimed indolyl derivatives are:



Compound	R1	R2	R3	R4	R5	R6	R7	R8	A	Formula
282581	H	H	F	H	H	H	H	2-Pyr	CH ₂	C ₂₁ H ₂₅ FN ₄
282582	H	H	H	H	H	-O-	-O-	2-Pyr	bond	C ₂₀ H ₂₂ N ₄ O
282583	H	H	H	bond	-O-	-O-	-O-	2-Pyr	bond	C ₂₀ H ₂₀ N ₄ O
282584	H	H	F	H	H	-O-	-O-	2,6-(Me)2-Ph	CH ₂	C ₂₄ H ₂₈ FN ₄ O
282585	H	Me	F	H	H	-O-	-O-	2-NO ₂ -Ph	CH ₂	C ₂₃ H ₂₅ FN ₄ O ₃
282586	H	H	OMe	H	H	H	H	4-F-Ph	CH ₂	C ₂₃ H ₂₈ FN ₄ O
282588	Me	H	OMe	H	H	-O-	-O-	2,6-(Cl)2-Ph	CH ₂	C ₂₄ H ₂₇ Cl ₂ N ₄ O ₂

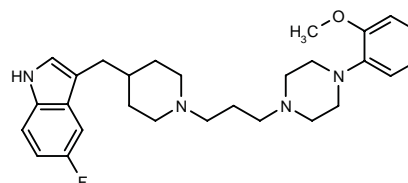
SOURCE – American Home Products.

REFERENCES

1. Kelly, M.G. and Kang, Y.H. (American Home Products Corp.) *Serotonergic agents*. WO 9955697.

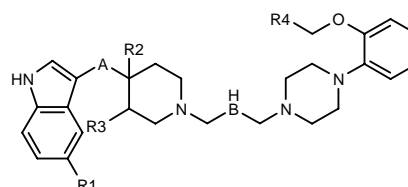
282591

5-Fluoro-3-[1-[3-[4-(2-methoxyphenyl)piperazin-1-yl]-propyl]piperidin-4-ylmethyl]-1*H*-indole



C₂₈ H₃₇ F N₄ O; Mol wt: 464.6253

ACTION – Serotonergic agent shown to act as a 5-HT reuptake inhibitor ($K_i = 1.2$ nM for inhibition of [³H]-paroxetine binding in rat cortical membranes). Particularly useful in the treatment of depression, as well as anxiety, drug withdrawal, eating and sexual disorders, etc. Other specifically claimed indolyl derivatives are:



Compound	R1	R2	R3	R4	A	B	Formula
282592	F	H	H	H	CH ₂	bond	C ₂₇ H ₃₅ FN ₄ O
282594	F	H	H	Me	CH ₂	bond	C ₂₈ H ₃₇ FN ₄ O
282595	F	H	H	Me	CH ₂	CH ₂	C ₂₉ H ₃₉ FN ₄ O
282599	H	H	H	H	bond	bond	C ₂₆ H ₃₄ N ₄ O
282600	H	bond	bond	H	bond	bond	C ₂₆ H ₃₂ N ₄ O
282601	F	bond	bond	H	bond	bond	C ₂₆ H ₃₁ FN ₄ O

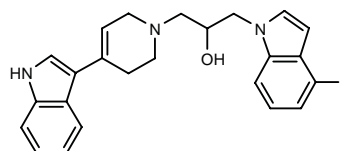
SOURCE – American Home Products.

REFERENCES

1. Kelly, M.G. and Kang, Y.H. (American Home Products Corp.) *Indolyl derivs. as serotonergic agents*. WO 9955695.

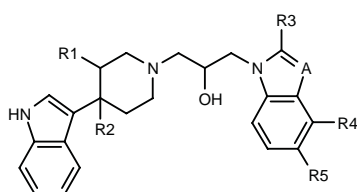
282602

1-(4-Fluoro-1*H*-indol-1-yl)-3-[4-(1*H*-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]propan-2-ol

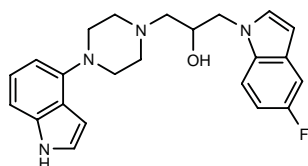
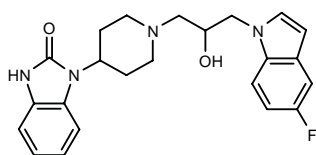


C₂₄ H₂₄ F N₃ O; Mol wt: 389.4716

ACTION – Serotonergic agent shown to act as a 5-HT reuptake inhibitor ($K_i = 0.01$ nM for inhibition of [³H]-paroxetine binding in rat cortical membranes). Particularly useful in the treatment of depression, as well as anxiety, drug withdrawal, eating and sexual disorders, etc. Other specifically claimed indolyl derivatives are:



Compound	R1	R2	R3	R4	R5	A	Isomer	Formula
282603	bond		H	H	F	CH		C ₂₄ H ₂₄ FN ₃ O
282604	H	H	H	H	F	CH		C ₂₄ H ₂₆ FN ₃ O
282608	bond		H	OMe	H	CH		C ₂₅ H ₂₇ N ₃ O ₂
282609	bond		H	H	H	CH		C ₂₄ H ₂₅ N ₃ O
282610	bond		Me	H	H	N		C ₂₄ H ₂₆ N ₄ O
282611	bond		H	OMe	H	CH	S	C ₂₅ H ₂₇ N ₃ O ₂
282613	bond		H	F	H	CH	S	C ₂₄ H ₂₄ FN ₃ O

**282605:** C₂₃ H₂₅ F N₄ O**282607:** C₂₃ H₂₅ F N₄ O₂

SOURCE – American Home Products.

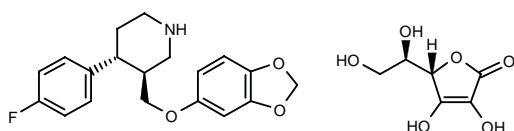
REFERENCES

- Kelly, M.G. and Kang, Y.H. (American Home Products Corp.) *Indolyl derivs. as serotonergic agents*. WO 9955694.

PAROXETINE ASCORBATE

282639

(3*S*,4*R*)-3-(1,3-Benzodioxol-5-yloxymethyl)-4-(4-fluorophenyl)piperidine D-ascorbate



C₁₉ H₂₀ F N O₃ . C₆ H₈ O₆; Mol wt: 505.4922

ACTION – Ascorbate salt of paroxetine⁺ that may be used as an alternative to the currently marketed hydrochloride in the treatment or prevention of CNS disorders such as depression, obsessive-compulsive disorder and panic, or as an intermediate in its preparation.

SOURCE – SmithKline Beecham.

REFERENCES

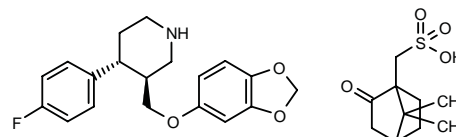
- Urquhart, M. (SmithKline Beecham plc) *Paroxetine ascorbate*. WO 9955698.

*Drug Data Rep 1991, 013(05): 0371.

PAROXETINE CAMSILATE

282640

(3*S*,4*R*)-3-(1,3-Benzodioxol-5-yloxymethyl)-4-(4-fluorophenyl)piperidine 10-camphorsulfonate



C₁₉ H₂₀ F N O₃ . C₁₀ H₁₆ O₄ S; Mol wt: 561.6674

ACTION – 10-Camphorsulfonate salt of paroxetine⁺ that may be used as an alternative to the currently marketed hydrochloride in the treatment or prevention of CNS disorders such as depression, obsessive-compulsive disorder and panic, or as an intermediate in its preparation.

SOURCE – SmithKline Beecham.

REFERENCES

- Urquhart, M. (SmithKline Beecham plc) *Paroxetine 10-camphorsulfonate for treatment of CNS disorders*. WO 9955699.

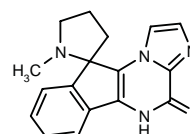
*Drug Data Rep 1991, 013(05): 0371.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

282054

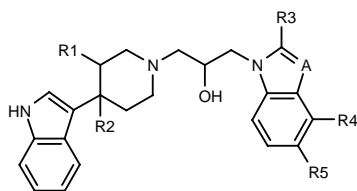
(+)-1'-Methylspiro[5,10-dihydro-4*H*-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-10,2'-pyrrolidin]-4-one



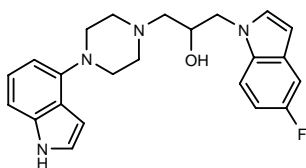
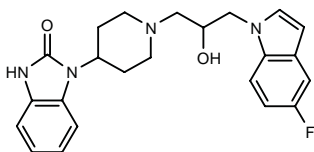
C₁₇ H₁₆ N₄ O; Mol wt: 292.3404

[α]_D²⁰ +32.4° (c 0.5, AcOH).

ACTION – Anticonvulsant with moderate affinity for both AMPA and glycine-site NMDA receptors (IC₅₀ = 86 and 172 nM, respectively). Compound showed good protection against maximal electroshock-induced convulsions in mice (ED₅₀ = 17 mg/kg i.p.) similar to YM-90K (ED₅₀ = 12 mg/kg i.p.) and 4-fold less active than LY-293558 (ED₅₀ = 4 mg/kg i.p.). It also had good activity following i.v. administration (ED₅₀ = 7 mg/kg).



Compound	R1	R2	R3	R4	R5	A	Isomer	Formula
282603	bond		H	H	F	CH		C ₂₄ H ₂₄ FN ₃ O
282604	H	H	H	H	F	CH		C ₂₄ H ₂₆ FN ₃ O
282608	bond		H	OMe	H	CH		C ₂₅ H ₂₇ N ₃ O ₂
282609	bond		H	H	H	CH		C ₂₄ H ₂₅ N ₃ O
282610	bond		Me	H	H	N		C ₂₄ H ₂₆ N ₄ O
282611	bond		H	OMe	H	CH	S	C ₂₅ H ₂₇ N ₃ O ₂
282613	bond		H	F	H	CH	S	C ₂₄ H ₂₄ FN ₃ O

**282605:** C₂₃ H₂₅ F N₄ O**282607:** C₂₃ H₂₅ F N₄ O₂

SOURCE – American Home Products.

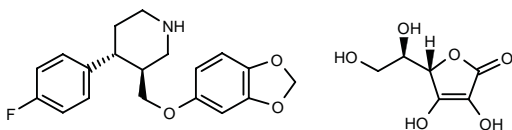
REFERENCES

- Kelly, M.G. and Kang, Y.H. (American Home Products Corp.) *Indolyl derivs. as serotonergic agents*. WO 9955694.

PAROXETINE ASCORBATE

282639

(3*S*,4*R*)-3-(1,3-Benzodioxol-5-yloxymethyl)-4-(4-fluorophenyl)piperidine D-ascorbate



C₁₉ H₂₀ F N O₃ . C₆ H₈ O₆; Mol wt: 505.4922

ACTION – Ascorbate salt of paroxetine⁺ that may be used as an alternative to the currently marketed hydrochloride in the treatment or prevention of CNS disorders such as depression, obsessive-compulsive disorder and panic, or as an intermediate in its preparation.

SOURCE – SmithKline Beecham.

REFERENCES

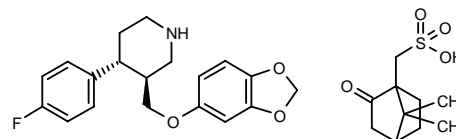
- Urquhart, M. (SmithKline Beecham plc) *Paroxetine ascorbate*. WO 9955698.

*Drug Data Rep 1991, 013(05): 0371.

PAROXETINE CAMSILATE

282640

(3*S*,4*R*)-3-(1,3-Benzodioxol-5-yloxymethyl)-4-(4-fluorophenyl)piperidine 10-camphorsulfonate



C₁₉ H₂₀ F N O₃ . C₁₀ H₁₆ O₄ S; Mol wt: 561.6674

ACTION – 10-Camphorsulfonate salt of paroxetine⁺ that may be used as an alternative to the currently marketed hydrochloride in the treatment or prevention of CNS disorders such as depression, obsessive-compulsive disorder and panic, or as an intermediate in its preparation.

SOURCE – SmithKline Beecham.

REFERENCES

- Urquhart, M. (SmithKline Beecham plc) *Paroxetine 10-camphorsulfonate for treatment of CNS disorders*. WO 9955699.

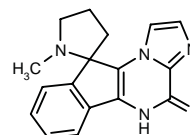
*Drug Data Rep 1991, 013(05): 0371.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

282054

(+)-1'-Methylspiro[5,10-dihydro-4*H*-imidazo[1,2-*a*]-indeno[1,2-*e*]pyrazin-10,2'-pyrrolidin]-4-one



C₁₇ H₁₆ N₄ O; Mol wt: 292.3404

[α]_D²⁰ +32.4° (c 0.5, AcOH).

ACTION – Anticonvulsant with moderate affinity for both AMPA and glycine-site NMDA receptors (IC₅₀ = 86 and 172 nM, respectively). Compound showed good protection against maximal electroshock-induced convulsions in mice (ED₅₀ = 17 mg/kg i.p.) similar to YM-90K (ED₅₀ = 12 mg/kg i.p.) and 4-fold less active than LY-293558 (ED₅₀ = 4 mg/kg i.p.). It also had good activity following i.v. administration (ED₅₀ = 7 mg/kg).

SOURCE – Aventis Pharma.

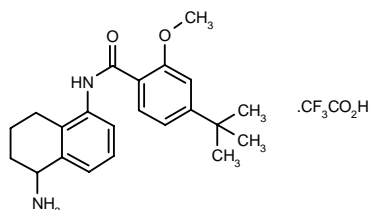
REFERENCES

1. Aloup, J.-C. et al. (Rhône-Poulenc Rorer SA) *Spiro[heterocycle-imidazo[1,2-a]indeno[1,2-e]pyrazine]-4'-ones, preparation thereof and drugs containing same*. JP 1998508311, US 5777114, WO 9614318.

2. Jimonet, P. et al. *Spiro-imidazo[1,2-a]indeno[1,2-e]pyrazine-4-one derivatives are mixed AMPA and NMDA glycine-site antagonists active in vivo*. Bioorg Med Chem Lett 1999, 9(20): 2921.

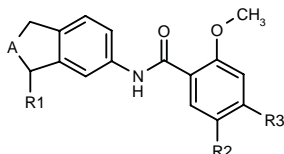
282240

N-(5-Amino-5,6,7,8-tetrahydronaphthalen-1-yl)-4-(*tert*-butyl)-2-methoxybenzamide trifluoroacetate

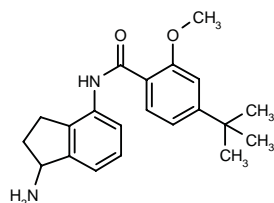


C22 H28 N2 O2 . C2 H F3 O2; Mol wt: 466.4971

ACTION – Anticonvulsant that binds to the same receptor as SB-204269 ($pK_i > 6.5$ against [3H]-SB-204269 binding in rat forebrain tissue preparations), reported to produce a 43% increase in seizure threshold at a dose of 10 mg/kg p.o. in the maximal electroshock seizure (MES) test in mice. It may also be useful in the treatment and/or prevention of other CNS disorders such as anxiety, depression, withdrawal from drugs of abuse, nicotine or alcohol, Parkinson's disease, psychosis, cerebral ischemia, pain and amyotrophic lateral sclerosis. Other specifically claimed compounds are:



Compound	R1	R2	R3	A	Formula
282241	H	Br	OMe	-CH(NH2)-	C ₁₈ H ₁₉ BrN ₂ O ₃
282242	H	Br	OMe	-CH[N(Me)2]-	C ₂₀ H ₂₃ BrN ₂ O ₃
282243	NH2	Br	OMe	-(CH2)2-	C ₁₉ H ₂₁ BrN ₂ O ₃
282244	N(Me)2	H	t-Bu	-(CH2)2-	C ₂₄ H ₃₂ N ₂ O ₂
282246	NH2	Br	OMe	-CH2-	C ₁₈ H ₁₉ BrN ₂ O ₃
282247	NHMe	H	t-Bu	-CH2-	C ₂₂ H ₂₈ N ₂ O ₂



282245: C21 H26 N2 O2

SOURCE – SmithKline Beecham.

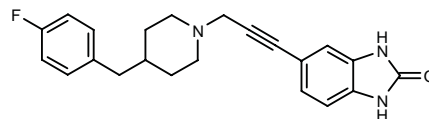
REFERENCES

1. Orlek, B.S. et al. (SmithKline Beecham plc) *Novel cpds*. WO 9952857.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

283034

5-[3-[4-(4-Fluorobenzyl)piperidin-1-yl]-1-propynyl]-1,3-dihydro-2H-benzimidazol-2-one



C22 H22 F N3 O; Mol wt: 363.4338

ACTION – Potent NMDA receptor antagonist selective for NR1A/2B ($IC_{50} = 10$ nM) over NR1A/2A and NR1A/2C subtypes ($IC_{50} = 25$ and > 300 μ M, respectively), as well as over α -adrenoceptors and dopamine D₂ receptors ($IC_{50} > 1$ μ M). Compound (30 mg/kg p.o.) was seen to potentiate the L-DOPA-induced increase in rotations in 6-OHDA-lesioned rats. Potentially useful for the treatment of Parkinson's disease.

SOURCES – CoCensys; Warner-Lambert.

REFERENCES

1. Bigge, C.F. et al. (Warner-Lambert Co.; CoCensys, Inc.) *4-Subst. piperidine analogs and their use as subtype selective NMDA receptor antagonists*. EP 0869791, WO 9723214.

2. Wright, J.L. et al. *1-(Heteroarylalkynyl)-4-benzylpiperidines as orally active subtype-selective NMDA antagonists for the treatment of Parkinson's disease*. Soc Neurosci Abstr 1999, 25(Part 2): Abstr 683.1.

COGNITION-ENHANCING DRUGS

281372

NH₂-Met-Leu-Gly-Ile-Phe-Arg-Leu-Ala-Ala-Ala-Glu-Asn-Pro-Ser-Ala-Val-Asn-Ala-Asn-Ala-Lys-Glu-Arg-Arg-Gly-Cys-Pro-Trp-Phe-Trp-Gln-Pro-Leu-Glu-Gly-Arg-Asp-Lys-Thr-Phe-Pro-Ala-Asp-Arg-Arg-Gly-Arg-Cys-Lys-Ser-Val-Phe-Trp-Lys-Leu-His-Trp-Cys-Ile-Phe-Ile-Ser-Phe-Ser-Met-Ala-OH

ACTION – Cardiostatin polypeptide that exhibits strong structural similarity to the somatostatin family of neuropeptides, with potential in the treatment of behavioral and cognitive disorders, dementia, blood pressure disorders, diabetes, renal failure, asthma, chronic obstructive pulmonary disease, congestive heart failure, ischemic heart disease, cardiac arrhythmias and stroke. Polynucleotides encoding this polypeptide, as well as their use in therapy or diagnosis or for identifying agonists, antagonists and/or inhibitors thereof for use in therapy are also disclosed.

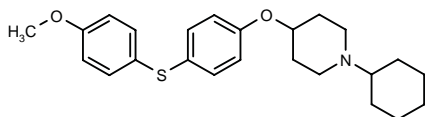
SOURCE – SmithKline Beecham.

REFERENCES

1. Arleth, A. et al. (SmithKline Beecham plc; SmithKline Beecham Corp.) *Cardiostatin polypeptides and polynucleotides*. WO 9949044.

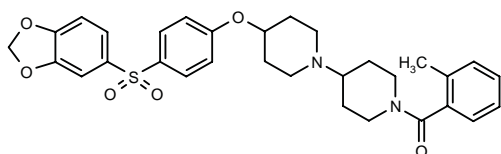
282294

1-Cyclohexyl-4-[4-(4-methoxyphenylsulfanyl)phenoxy]-piperidine



C₂₄ H₃₁ N O₂ S; Mol wt: 397.5799

ACTION – Muscarinic receptor antagonist with selectivity for M₂ and/or M₄ receptors and believed to be capable of enhancing acetylcholine release. Potentially useful in the treatment of cognitive and neurodegenerative disorders such as Alzheimer's disease, especially in combination with an acetylcholinesterase inhibitor. Another compound from this series of 1,4-disubstituted piperidine derivatives is:



282295: C₃₁ H₃₄ N₂ O₆ S

SOURCE – Schering-Plough.

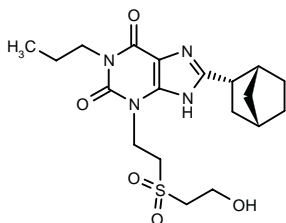
REFERENCES

1. Wang, Y. et al. (Schering Corp.) *Ether muscarinic antagonists*. US 5977138.

282311

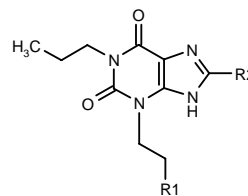
8-[(1*R*,2*S*,4*S*)-Bicyclo[2.2.1]hept-2-yl]-3-[2-(2-hydroxyethylsulfonyl)ethyl]-1-propyl-2,3,6,9-tetrahydro-1*H*-purine-2,6-dione

8-[(1*R*,2*S*,4*S*)-Bicyclo[2.2.1]hept-2-yl]-3-[2-(2-hydroxyethylsulfonyl)ethyl]-1-propylxanthine



C₁₉ H₂₈ N₄ O₅ S; Mol wt: 424.5192

ACTION – Selective adenosine A₁ receptor antagonist (K_i = 9.4 nM vs. 4670 nM for A₂ receptors) with potential in the treatment of neurodegenerative disorders such as cognition disorders, depression, asthma, ischemia and reperfusion injury, edema, heart failure, bradyarrhythmias and renal failure. Within this series of asymmetrically substituted xanthine derivatives, the following are also included:



Compound	R1	R2	Formula
282312	CONH ₂	t-Bu	C ₁₅ H ₂₃ N ₅ O ₃
282313	SO ₂ CH ₂ -CH ₂ OAc	(1 <i>R</i> ,2 <i>S</i> ,4 <i>S</i>)-bicyclo[2.2.1]hept-2-yl	C ₂₁ H ₃₀ N ₄ O ₆ S
282314	CONH ₂	(1 <i>R</i> ,2 <i>S</i> ,4 <i>S</i>)-bicyclo[2.2.1]hept-2-yl	C ₁₈ H ₂₅ N ₅ O ₃
282315	SO ₂ CH ₂ -CH ₂ OH	2-noradamantan-1-yl	C ₂₁ H ₃₀ N ₄ O ₅ S
282316	CONH ₂	2-noradamantan-1-yl	C ₂₀ H ₂₇ N ₅ O ₃

SOURCE – Boehringer Ingelheim.

REFERENCES

1. Blech, S. et al. (Boehringer Ingelheim Pharma KG) *Novel asymmetrically subst. xanthine derivs., method for producing them and their use as medicaments with an adenosine antagonistic effect*. DE 19816857, WO 9954331.

GANSTIGMINE HYDROCHLORIDE

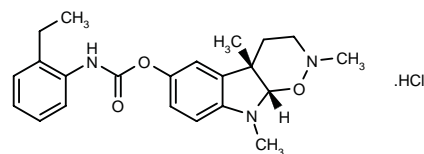
Prop INN

283070

N-(2-Ethylphenyl)carbamic acid (4*aS*,9*aS*)-2,4*a*,9-trimethyl-2,3,4,4*a*,9,9*a*-hexahydro[1,2]oxazino[6,5-*b*]indol-6-yl ester hydrochloride

N-(2-Ethylphenyl)geneserine hydrochloride

CHF-2819



C₂₂ H₂₇ N₃ O₃ · HCl; Mol wt: 417.9342

ACTION – Cognition-enhancing agent, a selective inhibitor of brain acetylcholinesterase (AChE), proven to inhibit rat brain AChE after oral administration with a maximum effect between 2 and 6 h (ED₅₀ = 1.5 mg/kg at 2 h). At doses of 0.5-4.5 mg/kg p.o., it significantly increased ACh concentrations in the hippocampus of both 2- and 18-month-old rats. Behavioral studies demonstrated its ability to reverse memory deficits induced by scopolamine in rat passive avoidance and Morris water-maze tests; in the latter paradigm, it had a bell-shaped dose-response curve, ameliorating memory deficits at the doses of 0.75 and 1.5 mg/kg p.o., but not at the higher dose of 3.0 mg/kg p.o. Potentially useful for the treatment of cognitive disturbances associated with Alzheimer's disease.

SOURCE – Chiesi.

REFERENCES

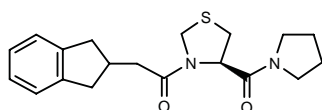
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- Villetti, G. et al. Cholinesterase inhibitory activity and anti-amnesic effect of CHF2819, a potential antidementia drug. Soc Neurosci Abst 1999, 25(Part 2): Abst 847.1.
- Proposed international nonproprietary names (Prop. INN): List 81. WHO Drug Inf 1999, 13(2): 116.

Z-321*

165270

1-[N-(2-Indanylacetyl)-4-thia-L-prolyl]pyrrolidine

1-[3-(2-Indanylacetyl)thiazolidin-4(R)-ylcarbonyl]-pyrrolidine



C19 H24 N2 O2 S; Mol wt: 344.4766

ACTION – Selective, orally active prolyl endopeptidase (PEP) inhibitor proven to inhibit the degradation of proline-containing neuropeptides such as arginine-vasopressin in dog brain. After oral administration, it dose-dependently inhibited brain PEP levels, prolonged survival time after hypoxia in mice, improved impaired step-down passive avoidance induced by cerebral ischemia in mice and ameliorated behavioral impairment in step-through passive avoidance induced by CO₂ or electroconvulsive shock in rats. The results of a human study in healthy male volunteers indicated an acceptable pharmacodynamic and pharmacokinetic profile for clinical use, and it was devoid of significant side effects; the dose of 60 mg b.i.d. was selected for further clinical studies. Potentially useful for the treatment of Alzheimer's disease and other dementias and for the prevention of memory loss.

SOURCE – Zeria.

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- Aotsuka, T. et al. (Zeria Pharmaceutical Co., Ltd.) Condensed benzene deriv. AU 8945914, EP 372484, JP 1990262557, US 5028604.
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- Miura, N. et al. Z-321, a prolyl endopeptidase inhibitor, augments the potentiation of synaptic transmission in rat hippocampal slices. Behav Brain Res 1997, 83(1-2): 213.
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11. Umemura, K. et al. Pharmacokinetics and safety of Z-321, a novel specific orally active prolyl endopeptidase inhibitor, in healthy male volunteers. J Clin Pharmacol 1999, 39(5): 462.

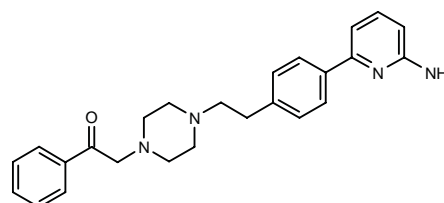
12. Zeria's R&D line-up. Kagaku Kogyo Nippo 1993, March 31.

*Identified compound **165270** (see **163731**) Drug Data Rep 1990, 012(10): 0770.

TREATMENT OF CEREBROVASCULAR DISEASES

280667

2-[4-[2-[4-(6-Aminopyridin-2-yl)phenyl]ethyl]piperazin-1-yl]-1-phenylethanone



C25 H28 N4 O; Mol wt: 400.5232

ACTION – Potent inhibitor of constitutive human nitric oxide synthase (NOS) with high selectivity for the neuronal (nNOS) versus the endothelial (eNOS) form (IC₅₀ = 140 and 887 nM, respectively) and showing negligible binding affinity for a panel of receptors except for muscarinic M₂ and M₄ receptors (K_i = 0.32 and 0.59 μM, respectively). Compound showed a good pharmacokinetic profile after s.c. administration in rats, providing brain drug levels above the nNOS IC₅₀ for at least 6 h. In addition, it had no effect on blood pressure or heart rate at doses of up to 100 mg/kg s.c. Potentially useful for the treatment of stroke, Parkinson's disease and pain.

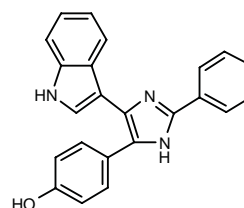
SOURCE – Pfizer.

REFERENCES

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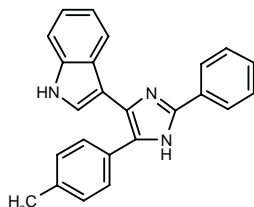
282080

4-[4-(1H-Indol-3-yl)-2-phenyl-1H-imidazol-5-yl]phenol



C23 H17 N3 O; Mol wt: 351.4073

ACTION – An inhibitor of Ca^{2+} /calmodulin-dependent phosphodiesterase (PDE1; 88% inhibition at 100 μM using bovine brain enzyme) with potential in the treatment of the sequelae of cerebral vasospasm, cerebrovascular dementia, senile dementia and cognitive disorders. Another compound from this series of 5-(substituted phenyl)-4-(3-indolyl)imidazole derivatives is:



282081: C₂₄ H₁₉ N₃

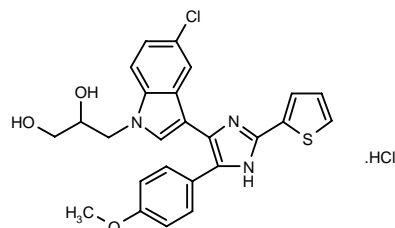
SOURCES – Sagami; Taisho.

REFERENCES

1. Ohta, T. et al. (Taisho Pharmaceutical Co., Ltd.;Sagami Chemical Research Center) 5-(Substd. phenyl)-4-(3-indolyl)imidazole derivs. JP 1999228570.

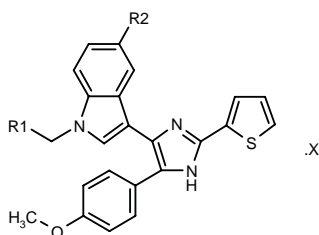
282082

3-[5-Chloro-3-[5-(4-methoxyphenyl)-2-(2-thienyl)-1H-imidazol-4-yl]-1H-indol-1-yl]-1,2-propanediol hydrochloride



C₂₅ H₂₂ Cl N₃ O₃ S . HCl; Mol wt: 516.4467

ACTION – An inhibitor of Ca^{2+} /calmodulin-dependent phosphodiesterase (PDE1; 92% inhibition at 10 μM using bovine brain enzyme) with potential in the treatment of the sequelae of cerebral vasospasm, cerebrovascular dementia, senile dementia and cognitive disorders. Other compounds from this series of 4-(3-indolyl)imidazole derivatives include the following:



Compound	R1	R2	X	Formula
282083	CH ₂ OH	Cl	HCl	C ₂₄ H ₂₀ ClN ₃ O ₂ S.HCl
282084	CO ₂ H	H		C ₂₄ H ₁₉ N ₃ O ₃ S
282085	CH ₂ NH ₂	Cl	2HCl	C ₂₄ H ₂₁ ClN ₄ O ₂ .2HCl
282086	CH ₂ NH ₂	OMe	2HCl	C ₂₅ H ₂₄ N ₄ O ₂ .2HCl

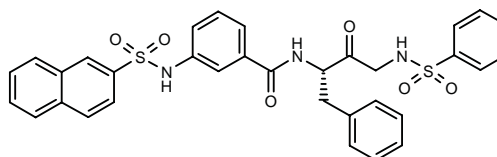
SOURCES – Sagami; Taisho.

REFERENCES

1. Ohta, T. et al. (Taisho Pharmaceutical Co., Ltd.;Sagami Chemical Research Center) 4-(3-Indolyl)imidazole derivs. JP 1999228572.

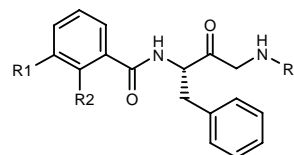
282282

3-(2-Naphthylsulfonamido)-N-[1(S)-benzyl-2-oxo-3-(phenylsulfonamido)propyl]benzamide



C₃₃ H₂₉ N₃ O₆ S₂; Mol wt: 627.7391

ACTION – An inhibitor of cysteine proteases such as calpain I ($\text{IC}_{50} < 1 \mu\text{M}$) and II and cathepsin B and L reported to possess improved water solubility over prior inhibitors and which is thus suitable for intravenous use. Potentially useful in the treatment of neurodegenerative disorders, cerebral ischemia, stroke, cardiac or renal ischemia, reperfusion injury, inflammation, rheumatoid arthritis, muscular dystrophy, restenosis following angioplasty, coronary or cerebral vasospasm, cataracts and cancer. A representative compound from a series of substituted benzamides, wherein the following are also included:



Compound	R1	R2	R3	Formula
282283	H	(E)-4-Pyr-CH=CH	SO ₂ Ph	C ₃₀ H ₂₇ N ₃ O ₄ S
282284	H	(E)-4-Pyr-CH=CH	SO ₂ Me	C ₂₅ H ₂₅ N ₃ O ₄ S
282285	2-Naph-SO ₂ NH	H	SO ₂ Me	C ₂₈ H ₂₇ N ₃ O ₆ S ₂
282286	2-Naph-SO ₂ NH	H	COPh	C ₃₄ H ₂₉ N ₃ O ₅ S
282287	H	(E)-4-Pyr-CH=CH	COPh	C ₃₁ H ₂₇ N ₃ O ₃

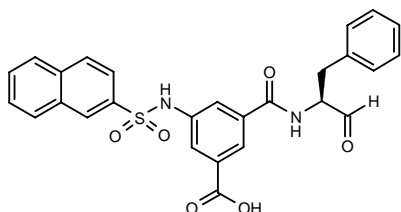
SOURCE – BASF.

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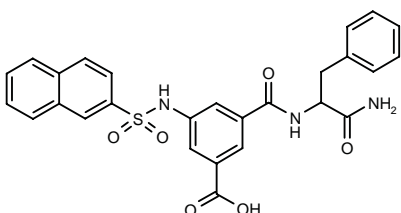
282332

3-[N-[1(S)-Formyl-2-phenylethyl]carbamoyl]-5-(2-naphthylsulfonamido)benzoic acid



C27 H22 N2 O6 S; Mol wt: 502.5448

ACTION – An inhibitor of cysteine proteases such as calpain I and II and cathepsin B and L reported to possess improved water solubility over prior inhibitors and which is thus suitable for intravenous use. Potentially useful in the treatment of neurodegenerative disorders, cerebral ischemia, stroke, cardiac or renal ischemia, reperfusion injury, inflammation, rheumatoid arthritis, muscular dystrophy, restenosis following angioplasty, coronary or cerebral vasospasm, cataracts and cancer. Another exemplified compound within this series of substituted amides is:



282333: C27 H23 N3 O6 S

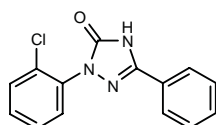
SOURCE – BASF.

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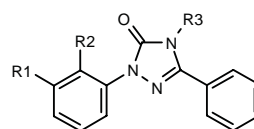
282334

1-(2-Chlorophenyl)-3-phenyl-4,5-dihydro-1H-1,2,4-triazol-5-one



C14 H10 Cl N3 O; Mol wt: 271.7060

ACTION – Neuroprotective agent, an AMPA receptor antagonist reported to exhibit high affinity for the Na⁺ channel site 2 and proven to inhibit kainate-induced currents in neuronal cells by 97% at 100 μM. Other exemplified compounds within this series of triazolone derivatives include the following:



Compound	R1	R2	R3	Formula
282335	H	Br	Me	C ₁₅ H ₁₂ BrN ₃ O
282336	H	F	H	C ₁₄ H ₁₀ FN ₃ O
282337	F	H	Me	C ₁₅ H ₁₂ FN ₃ O
282338	H	Cl	Me	C ₁₅ H ₁₂ ClN ₃ O
282340	H	Br	H	C ₁₄ H ₁₀ BrN ₃ O
282341	H	Me	CH ₂ CH ₂ N(Me) ₂	C ₁₉ H ₂₂ N ₄ O

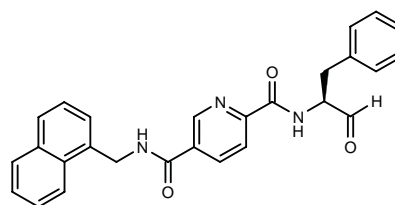
SOURCE – Boehringer Ingelheim.

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1. Brenner, M. et al. (Boehringer Ingelheim Pharma KG) *Triazolones with a neuroprotective action*. DE 19816882, WO 9954315.

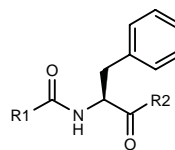
282339

N²-[1(S)-Benzyl-2-oxoethyl]-N⁵-(1-naphthylmethyl)-pyridine-2,5-dicarboxamide



C27 H23 N3 O3; Mol wt: 437.4967

ACTION – An inhibitor of cysteine proteases such as calpain I and II and cathepsin B and L with potential in the treatment of neurodegenerative disorders, cerebral ischemia, stroke, cardiac or renal ischemia, reperfusion injury, inflammation, rheumatoid arthritis, muscular dystrophy, restenosis following angioplasty, coronary or cerebral vasospasm, cataracts and cancer. A representative compound from a series of heterocyclically substituted amides, wherein the following are also included:



Compound	R1	R2	Formula
282342	6-(2-Naph-SO ₂ NH)-3-Pyr	H	C ₂₅ H ₂₁ N ₃ O ₄ S
282343	6-(2-Naph-CONH)-3-Pyr	H	C ₂₆ H ₂₁ N ₃ O ₃
282344	2-(2-Naph-SO ₂ NH)-5-Cl-4-pyrimidinyl	H	C ₂₄ H ₁₉ ClN ₄ O ₄ S
282345	2-(2-Naph-SO ₂ NH)-5-Cl-4-pyrimidinyl	CONH ₂	C ₂₅ H ₂₀ ClN ₅ O ₄ S
282346	2-(2-Naph-CONH)-4-thiazolyl	H	C ₂₄ H ₁₉ N ₃ O ₃ S
282347	2-(2-Naph-CONH)-4-thiazolyl	CONH ₂	C ₂₅ H ₂₀ N ₄ O ₄ S
282348	1-(2-Naph-CH ₂)-4-Me-5-imidazolyl	CONH ₂	C ₂₆ H ₂₄ N ₄ O ₃
282349	1-(2-Naph-CH ₂)-2-Me-5-imidazolyl	CONH ₂	C ₂₆ H ₂₄ N ₄ O ₃
282350	1-(2-Naph-CH ₂)-2-imidazolyl	CONH ₂	C ₂₅ H ₂₂ N ₄ O ₃
282351	1-(CH ₂ Ph)-2-imidazolyl	CONH ₂	C ₂₁ H ₂₀ N ₄ O ₃
282353	1-(2-Naph-CH ₂)-5-imidazolyl	CONH ₂	C ₂₅ H ₂₂ N ₄ O ₃
282354	2-(2-Naph-CH=CH)-3-Pyr	H	C ₂₇ H ₂₂ N ₂ O ₂
282356	2-(4-Pyr-CH=CH)-3-Pyr	H	C ₂₂ H ₁₉ N ₃ O ₂

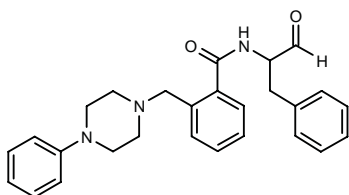
SOURCE – BASF.

REFERENCES

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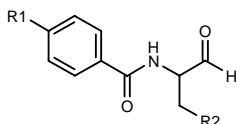
282393

N-(1-Benzyl-2-oxoethyl)-2-(4-phenylpiperazin-1-ylmethyl)benzamide

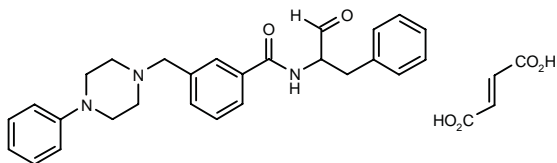


C27 H29 N3 O2; Mol wt: 427.5451

ACTION – An inhibitor of cysteine proteases such as calpain I and II and cathepsin B and L reported to possess improved water solubility over prior inhibitors and which is thus suitable for intravenous use. Potentially useful in the treatment of neurodegenerative disorders, cerebral ischemia, stroke, cardiac or renal ischemia, reperfusion injury, inflammation, rheumatoid arthritis, muscular dystrophy, restenosis following angioplasty, coronary or cerebral vasospasm, cataracts and cancer. A representative compound from a series of heterocyclically substituted amides, wherein the following are also included:



Compound	R1	R2	Formula
282396	CH2N(Me)CH2Ph	Me	C ₂₀ H ₂₄ N ₂ O ₂
282397	4-MeO-PhCH2N(Me)CH2	cyclohexyl	C ₂₆ H ₃₄ N ₂ O ₃
282398	1,2,3,4-tetrahydro-1-quinolyl-CH2	Ph	C ₂₆ H ₂₆ N ₂ O ₂
282399	6,7-(MeO)2-1,2,3,4-tetrahydro-2-isoquinolyl-CH2	cyclohexyl	C ₂₈ H ₃₆ N ₂ O ₄



282395: C27 H29 N3 O2 . C4 H4 O4

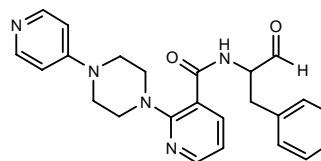
SOURCE – BASF.

REFERENCES

1. Lubisch, W. et al. (BASF AG) *Novel heterocyclically subst. amides with cysteine protease-inhibiting effect*. WO 9954320.

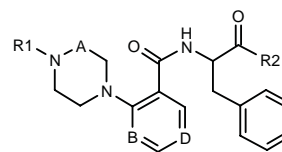
282400

N-(1-Benzyl-2-oxoethyl)-2-[4-(4-pyridyl)piperazin-1-yl]pyridine-3-carboxamide

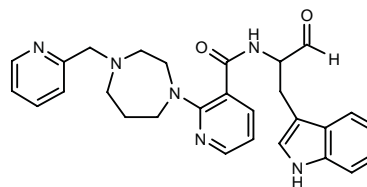


C24 H25 N5 O2; Mol wt: 415.4945

ACTION – An inhibitor of cysteine proteases such as calpain I and II and cathepsin B and L reported to possess improved water solubility over prior inhibitors and which is thus suitable for intravenous use. Potentially useful in the treatment of neurodegenerative disorders, cerebral ischemia, stroke, cardiac or renal ischemia, reperfusion injury, inflammation, rheumatoid arthritis, muscular dystrophy, restenosis following angioplasty, coronary or cerebral vasospasm, cataracts and cancer. A representative compound from a series of heterocyclically substituted amides, wherein the following are also included:



Compound	R1	R2	A	B	D	Formula
282401	CH2Ph	H	-CH2-	N	CH	C ₂₆ H ₂₈ N ₄ O ₂
282402	4-Pyr-CH2	H	-(CH2)2-	N	CH	C ₂₆ H ₂₉ N ₅ O ₂
282403	4-N(Me)2-PhCH2	H	-(CH2)2-	N	CH	C ₂₉ H ₃₅ N ₅ O ₂
282404	4-MeO-PhCH2	H	-(CH2)2-	N	CH	C ₂₈ H ₃₂ N ₄ O ₃
282405	3-Me-Ph	H	-(CH2)2-	N	CH	C ₂₇ H ₃₀ N ₄ O ₂
282406	CH2Ph	CONH2	-CH2-	CH	CH	C ₂₆ H ₃₀ N ₄ O ₃
282408	CH2Ph	2-Pyr-CH2-CH2NHCO	-CH2-	N	CH	C ₃₄ H ₃₆ N ₆ O ₃
282409	Ph	CONH2	-CH2-	CH	C(NO2)	C ₂₇ H ₂₇ N ₅ O ₅
282410	CH2Ph	CONH2	-CH2-	CH	N	C ₂₇ H ₂₉ N ₅ O ₃

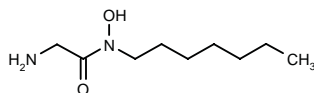


282411: C28 H30 N6 O2

SOURCE – BASF.

REFERENCES

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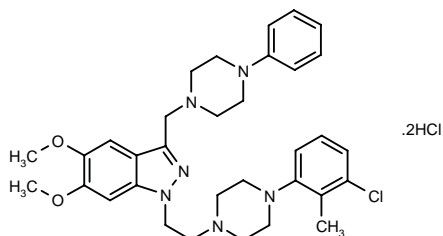
282675**2-Amino-N-heptylacetohydroxamic acid**

C9 H20 N2 O2; Mol wt: 188.2690

ACTION – Potent and selective ligand for the glycine site of the NMDA receptor ($IC_{50} = 4.5 \mu M$ for displacement of [3H]-glycine binding in rat cortical membranes) with weaker affinity for glutamate sites ($IC_{50} = 16 \mu M$ for displacement of [3H]-CGS-19755 binding) and no affinity (up to $1 \mu M$) for kainate and AMPA sites. In *in vitro* functional studies in guinea pig ileum/myenteric plexus preparations, compound inhibited NMDA-induced contractions. Potentially useful as a neuroprotective or anticonvulsant agent.

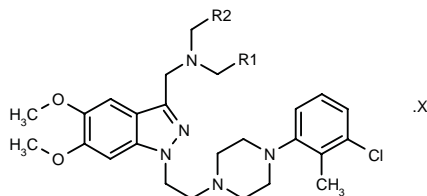
SOURCE – Chiesi.**REFERENCES**

1. Ghidini, E. et al. Synthesis of a new series of N-hydroxy, N-alkylamides of aminoacids as ligands of NMDA glycine site. Eur J Med Chem 1999, 34(9): 711.

283951**1-[2-[4-(3-Chloro-2-methylphenyl)piperazin-1-yl]ethyl]-5,6-dimethoxy-3-(4-phenylpiperazin-1-ylmethyl)-1H-indazole dihydrochloride**

C33 H41 Cl N6 O2 . 2HCl; Mol wt: 662.1017

ACTION – Agent for the treatment of cerebrovascular disorders, a calmodulin inhibitor whose activity was demonstrated *in vitro* by inhibition of calmodulin-dependent phosphodiesterase activity (94% inhibition at $5 \mu M$). Within this series of indazole derivatives, the following are also included:



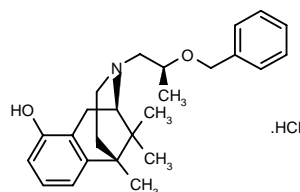
Compound	R1	R2	X	Formula
283952	CH ₂ CH ₂ OMe	Bu	2HCl	C ₃₂ H ₄₈ ClN ₅ O ₃ ·2HCl
283953	CH ₂ OH	Ph	2HCl	C ₃₂ H ₄₀ ClN ₅ O ₃ ·2HCl
283954	-CH ₂ N(Me)CH ₂ -		3HCl	C ₂₈ H ₃₉ ClN ₆ O ₂ ·3HCl

SOURCE – Daiichi Pharmaceutical.**REFERENCES**

1. Yokohama, S. et al. (Daiichi Pharmaceutical Co., Ltd.) Indazole derivs. JP 1999279156.

BIII-890-CL***283169****275626** (as free base)

(2*R*,6*S*)-3-[2(*S*)-Benzyloxypropyl]-6,11,11-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-10-ol hydrochloride



C25 H33 N O2 . HCl; Mol wt: 416.0016

ACTION – Potent and selective voltage-dependent sodium channel blocker proven to displace [3H]-batrachotoxin from site 2 of the Na⁺ channel with a K_i value of 40 nmol/l, while having no affinity for the tetrodotoxin binding site; compound also showed weak affinity for the verapamil and diltiazem site of the L-type Ca²⁺ channel ($K_i = 449$ and 660 nmol/l, respectively) and for σ -, κ - and μ -opiate receptors ($IC_{50} = 1-3 \mu mol/l$). It inhibited veratridine-induced glutamate release from rat brain cortical and striatal slices ($IC_{50} = 285$ and 326 nmol/l, respectively) and prevented veratridine-induced glutamate release and neurotoxicity in serum-free cultures of cortical neurons with an approximate IC_{50} of 1 $\mu mol/l$. Electrophysiological studies on cloned rat Na⁺ channel α -subunits demonstrated that it is a highly use-dependent Na⁺ channel blocker that preferentially binds to the inactivated state of the channel. In models of permanent focal cerebral ischemia (unilateral occlusion of the middle cerebral artery) in rats and mice, compound given s.c. at doses of 3-30 mg/kg significantly and dose-dependently reduced infarct size even when treatment was delayed for up to 2 h after ischemia. When infused i.v. in rats with permanent and transient focal cerebral ischemia, it produced significant and dose-dependent reductions in infarct volume in both cortical and subcortical regions and was more active than aptiganel. Currently undergoing clinical evaluation as a treatment for acute thrombotic stroke.

SOURCE – Boehringer Ingelheim.**REFERENCES**

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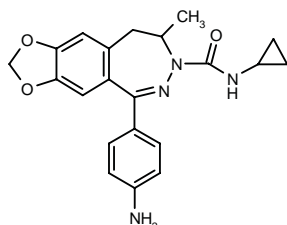
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*Identified compound **275626** Drug Data Rep 1999, 021(07): 0587.

EGIS-9637*

273859

(±)-5-(4-Aminophenyl)-N-cyclopropyl-8-methyl-8,9-dihydro-7H-[1,3]dioxolo[4,5-*h*][2,3]benzodiazepine-7-carboxamide



C21 H22 N4 O3; Mol wt: 378.4298

ACTION – Competitive AMPA/kainate receptor antagonist proven to inhibit kainate-evoked currents ($IC_{50} = 2.1 \mu M$) and AMPA/kainate-mediated toxicity ($IC_{50} = 13 \mu M$) in cultured neurons, as well as population spikes in rat hippocampal slices ($IC_{50} = 3.8 \mu M$). Compound protected against CA1 neuronal death (56% at 20 mg/kg i.p.) and reduced behavioral impairment in a model of global cerebral ischemia (bilateral carotid artery occlusion) in gerbils, and it exerted significant protection in a model of transient cerebral ischemia (middle cerebral artery occlusion) in mice. Compound also exhibited strong anticonvulsant activity in various seizure models. Potentially useful for the treatment of ischemic brain diseases.

SOURCE – Egis.

REFERENCES

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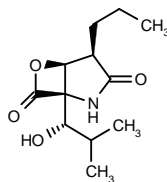
*Identified compound **273859** Drug Data Rep 1999, 021(05): 0400.

LDP-519

266388

(1*R*,4*R*,5*S*)-1-[1(*S*)-Hydroxy-2-methylpropyl]-4-propyl-6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione

PS-519



C12 H19 N O4; Mol wt: 241.2851

ACTION – Potent and selective proteasome inhibitor, an analogue of *clasto*-lactacystin β -lactone that acts as a potent inactivator of chymotrypsin-like activity of PA28-activated 20S proteasome. It has demonstrated neuroprotective, cardioprotective and antiinflammatory effects in animal models and is potentially useful in the treatment of stroke, myocardial infarction, multiple sclerosis and asthma.

SOURCE – LeukoSite (Millennium).

REFERENCES

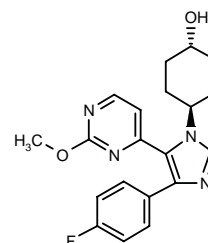
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9. Phillips, J.B. et al. *A novel proteasome inhibitor, PS519, shows neuroprotective efficacy in a rat model of transient focal ischemia*. FASEB J 1999, 13(5, Part 2): Abst 817.3.
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SB-239063*

254152

trans-4-[4-(4-Fluorophenyl)-5-(2-methoxypyrimidin-4-yl)imidazol-1-yl]cyclohexanol

trans-4-(4-Fluorophenyl)-1-(4-hydroxycyclohexyl)-5-(2-methoxypyrimidin-4-yl)imidazole



C20 H21 F N4 O2; Mol wt: 368.4100

ACTION – Neuroprotective agent, a potent inhibitor of p38 MAP kinase ($IC_{50} = 44$ nM) with at least 500-fold selectivity against a panel of other kinases. In middle cerebral artery occlusion (MCAO) models of moderate and severe brain injury in rats, compound infused i.v. 15 min after stroke and for 6 h to provide plasma levels of 0.38, 0.75 and 1.5 μ g/ml afforded significant protection against brain injury (reduction of total infarct volume) and neurological deficits.

SOURCE – SmithKline Beecham.

REFERENCES

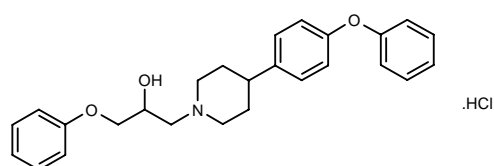
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- Adams, J.L. et al. (SmithKline Beecham plc) *Novel cycloalkyl subst. imidazoles*. EP 889726, WO 9725048.
- Alvi, S.A. *Use of CSAID(TM) cpds. for the management of uterine contractions*. WO 9918942.
- Feuerstein, G.Z. (SmithKline Beecham plc) *Novel treatment for CNS injuries*. EP 889888, WO 9735856.
- Horowitz, D. and King, A.G. (SmithKline Beecham Corp.) *Methods for reversibly inhibiting myelopoiesis in mammalian tissue*. WO 9816230.
- Barone, F.C. et al. *p38 MAPK in focal stroke: Selective inhibitor reduces brain injury and neurological deficits*. Soc Neurosci Abst 1999, 25(Part 1): Abst 433.2.
- Legos, J.J. et al. *Inhibition of p38 mitogen-activated protein kinase stroke: Neuroprotection confirmed using histopathology, MRI, and neurologic deficit analyses*. Stroke 2000, 31(1): Abst 34.

*Identified compound **254152** Drug Data Rep 1997, 019(10): 0932.

SUN-N5030

282061

1-Phenoxy-3-[4-(4-phenoxyphenyl)piperidin-1-yl]-2-propanol hydrochloride



C26 H29 N O3 . HCl; Mol wt: 439.9800

ACTION – Dual Na^+ and T-type Ca^{2+} channel blocker with IC_{50} values of 0.22 and 3.5 μ M, respectively, for inhibition of veratridine-induced depolarization in rat cerebrocortical synaptosomes and of T-type Ca^{2+} currents in primary cultures of rat cerebrocortical neurons, and low affinity for dopamine D_2 receptors ($IC_{50} = 4.64$ μ M). Compound showed a potent anticonvulsant effect in mice ($ED_{50} = 5$ mg/kg i.p. against audiogenic seizures) and neuroprotective activity in a model of transient middle cerebral artery occlusion in rats, as determined by reduction in peripheral-type benzodiazepine binding site densities in ipsilateral cortical and striatal homogenates at 10 days after reperfusion (65.8% reduction at 3 mg/kg i.v. immediately after MCAO and reperfusion). Neuroprotective doses of compound were not associated with effects on systemic blood pressure or heart rate in rats.

SOURCE – Suntory.

REFERENCES

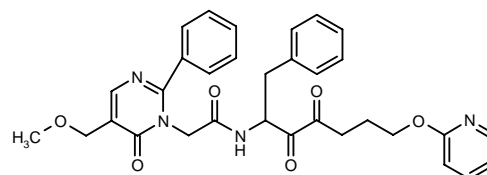
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RESPIRATORY DRUGS

ASTHMA THERAPY

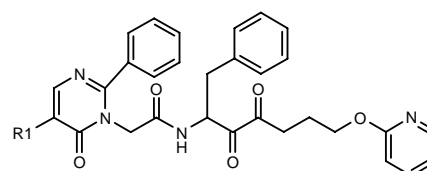
282025

N-[1-Benzyl-2,3-dioxo-6-(2-pyridyloxy)hexyl]-2-[5-(methoxymethyl)-6-oxo-2-phenyl-1,6-dihydropyrimidin-1-yl]acetamide



C32 H32 N4 O6; Mol wt: 568.6268

ACTION – An inhibitor of chymotrypsin-type proteases, particularly chymase, with IC_{50} values of 22 and 2.0 nM, respectively, against human and dog chymase. Potentially useful for the treatment of asthma, restenosis following angioplasty and atherosclerosis. Other compounds from this series of acetamide derivatives include the following:



Compound	R1	Formula
282027	CH2OAc	C ₃₃ H ₃₂ N ₄ O ₇
282028	CH2OH	C ₃₁ H ₃₀ N ₄ O ₆
282030	CO2Et	C ₃₃ H ₃₂ N ₄ O ₇

SOURCE – Nippon Kayaku.

REFERENCES

- Ishida, K. and Suzuki, Y. (Nippon Kayaku Co., Ltd.) *Novel acetamide deriv. and use thereof*. WO 9941277.

ACTION – Neuroprotective agent, a potent inhibitor of p38 MAP kinase (IC_{50} = 44 nM) with at least 500-fold selectivity against a panel of other kinases. In middle cerebral artery occlusion (MCAO) models of moderate and severe brain injury in rats, compound infused i.v. 15 min after stroke and for 6 h to provide plasma levels of 0.38, 0.75 and 1.5 µg/ml afforded significant protection against brain injury (reduction of total infarct volume) and neurological deficits.

SOURCE – SmithKline Beecham.

REFERENCES

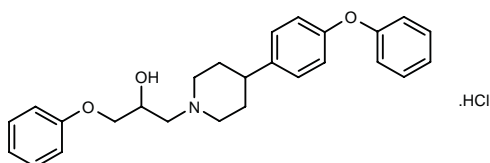
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- Adams, J.L. et al. (SmithKline Beecham Corp.) *Novel cycloalkyl substd. imidazoles*. WO 9901452.
- Adams, J.L. et al. (SmithKline Beecham plc) *Novel cycloalkyl substd. imidazoles*. EP 889726, WO 9725048.
- Alvi, S.A. *Use of CSAID(TM) cpds. for the management of uterine contractions*. WO 9918942.
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- Barone, F.C. et al. *p38 MAPK in focal stroke: Selective inhibitor reduces brain injury and neurological deficits*. Soc Neurosci Abst 1999, 25(Part 1): Abst 433.2.
- Legos, J.J. et al. *Inhibition of p38 mitogen-activated protein kinase stroke: Neuroprotection confirmed using histopathology, MRI, and neurologic deficit analyses*. Stroke 2000, 31(1): Abst 34.

*Identified compound **254152** Drug Data Rep 1997, 019(10): 0932.

SUN-N5030

282061

1-Phenoxy-3-[4-(4-phenoxyphenyl)piperidin-1-yl]-2-propanol hydrochloride



C26 H29 N O3 . HCl; Mol wt: 439.9800

ACTION – Dual Na^+ and T-type Ca^{2+} channel blocker with IC_{50} values of 0.22 and 3.5 µM, respectively, for inhibition of veratridine-induced depolarization in rat cerebrocortical synaptosomes and of T-type Ca^{2+} currents in primary cultures of rat cerebrocortical neurons, and low affinity for dopamine D_2 receptors (IC_{50} = 4.64 µM). Compound showed a potent anticonvulsant effect in mice (ED_{50} = 5 mg/kg i.p. against audiogenic seizures) and neuroprotective activity in a model of transient middle cerebral artery occlusion in rats, as determined by reduction in peripheral-type benzodiazepine binding site densities in ipsilateral cortical and striatal homogenates at 10 days after reperfusion (65.8% reduction at 3 mg/kg i.v. immediately after MCAO and reperfusion). Neuroprotective doses of compound were not associated with effects on systemic blood pressure or heart rate in rats.

SOURCE – Suntory.

REFERENCES

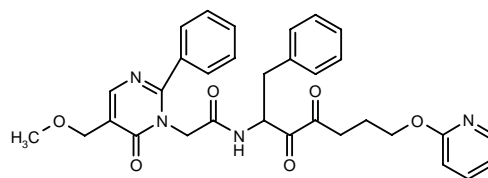
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RESPIRATORY DRUGS

ASTHMA THERAPY

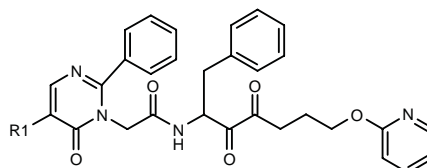
282025

N-[1-Benzyl-2,3-dioxo-6-(2-pyridyloxy)hexyl]-2-[5-(methoxymethyl)-6-oxo-2-phenyl-1,6-dihydropyrimidin-1-yl]acetamide



C32 H32 N4 O6; Mol wt: 568.6268

ACTION – An inhibitor of chymotrypsin-type proteases, particularly chymase, with IC_{50} values of 22 and 2.0 nM, respectively, against human and dog chymase. Potentially useful for the treatment of asthma, restenosis following angioplasty and atherosclerosis. Other compounds from this series of acetamide derivatives include the following:



Compound	R1	Formula
282027	CH2OAc	C ₃₃ H ₃₂ N ₄ O ₇
282028	CH2OH	C ₃₁ H ₃₀ N ₄ O ₆
282030	CO2Et	C ₃₃ H ₃₂ N ₄ O ₇

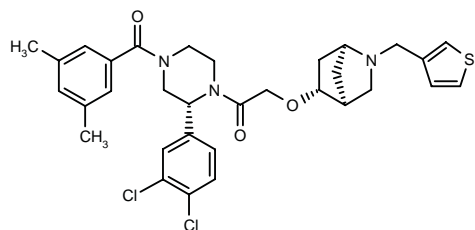
SOURCE – Nippon Kayaku.

REFERENCES

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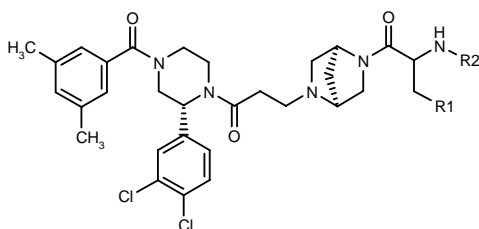
282159

1-[2(*R*)-(3,4-Dichlorophenyl)-4-(3,5-dimethylbenzoyl)piperazin-1-yl]-2-[(1*S*,4*S*,5*R*)-2-(3-thienylmethyl)-2-azabicyclo[2.2.1]hept-5-yloxy]-1-ethanone

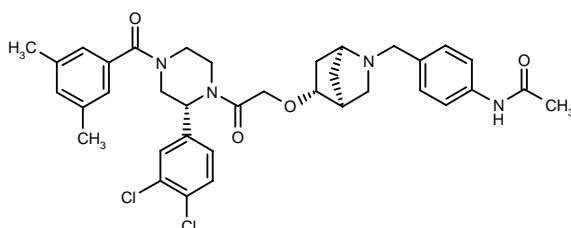


C32 H35 Cl2 N3 O3 S; Mol wt: 612.6185

ACTION – Neurokinin receptor antagonist with high affinity for both NK₁ and NK₂ receptors ($K_i = 1.8$ and 2.6 nM, respectively) in a receptor binding assay. It is expected to be useful for treating asthma, bronchospasm, allergies, anxiety, depression, cough or pain. Other exemplified piperazino derivatives include the following:



Compound	R1	R2	Isomer	Formula
282160	2-thienyl	H	S	C ₃₄ H ₃₉ Cl ₂ N ₅ O ₃ S
282161	Ph	CONHMe	R	C ₃₈ H ₄₄ Cl ₂ N ₆ O ₄



282162: C36 H40 Cl2 N4 O4

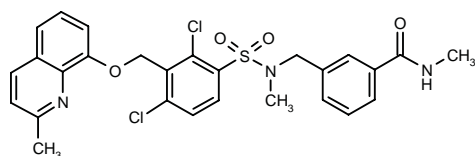
SOURCE – Schering-Plough.

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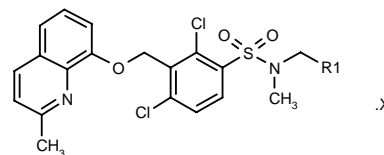
282171

3-[*N*-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)-phenylsulfonyl]-*N*-methylaminomethyl]-*N*-methylbenzamide



C27 H25 Cl2 N3 O4 S; Mol wt: 558.4835

ACTION – Bradykinin receptor antagonist found to inhibit [³H]-bradykinin binding to guinea pig B₂ receptors by 100% at a concentration of 1 μM and thus expected to have therapeutic potential in painful and inflammatory conditions, and especially for the treatment of asthma and allergic rhinitis. Other exemplified benzenesulfonamide derivatives include the following:



Compound	R1	X	Formula
282172	4-NH2-Ph	2HCl	C ₂₅ H ₂₃ Cl ₂ N ₃ O ₃ S·2ClH
282174	4-OH-Ph		C ₂₅ H ₂₂ Cl ₂ N ₃ O ₄ S
282177	3-(NH2CO)-Ph		C ₂₆ H ₂₃ Cl ₂ N ₃ O ₄ S
282178	3-[HO(CH2)3NHCO]-Ph		C ₂₉ H ₂₉ Cl ₂ N ₃ O ₅ S
282179	3-[N(Me)2CH2CH2NHCO]-Ph		C ₃₀ H ₃₂ Cl ₂ N ₄ O ₄ S
282181	(CH2)6NH2	2CF3CO2H	C ₂₅ H ₃₁ Cl ₂ N ₃ O ₃ S·2C ₂ HF ₃ O ₂
282182	(CH2)4CONHMe		C ₂₅ H ₂₉ Cl ₂ N ₃ O ₄ S

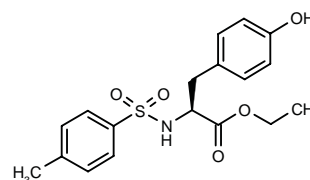
SOURCE – Fournier.

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- Dodey, P. et al. (Fournier Industrie et Santé) *Benzenesulfonamide derivs. as bradykinin antagonists*. FR 2735128, US 5968951, WO 9640639.

282642

N-(4-Methylphenylsulfonyl)-L-tyrosine ethyl ester



C18 H21 N O5 S; Mol wt: 363.4319

ACTION – Chemokine CCR3 receptor antagonist with potential in the treatment of bronchial asthma, eczema, conjunctivitis, allergic rhinitis, nasal polyposis, atopic dermatitis, pruritus and inflammatory bowel disease.

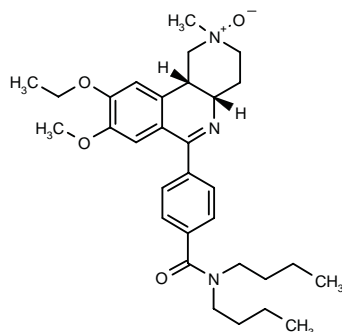
SOURCE – SmithKline Beecham.

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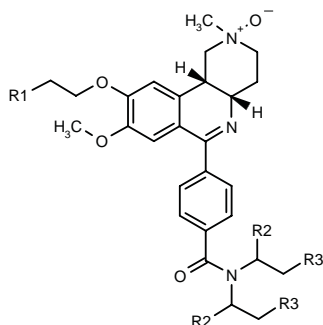
282771

cis-*N,N*-Dibutyl-4-(9-ethoxy-8-methoxy-2-methyl-2-oxido-1,2,3,4,4a,10b-hexahydrobenzo[*c*][1,6]naphthyridin-6-yl)benzamide



C31 H43 N3 O4; Mol wt: 521.6977

ACTION – Bronchodilating agent, a phosphodiesterase (PDE) inhibitor with selectivity for PDE4 ($-\log IC_{50} = 7.98$) over PDE3 ($-\log IC_{50} = 5.97$). Other compounds from this series of *N*-oxide derivatives include the following:



Compound	R1	R2	R3	Formula
282772	H	Me	H	C ₂₉ H ₃₉ N ₃ O ₄
282773	Me	H	Et	C ₃₂ H ₄₅ N ₃ O ₄

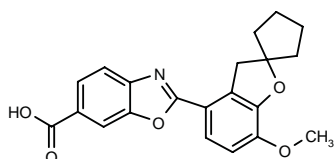
SOURCE – Byk Gulden.

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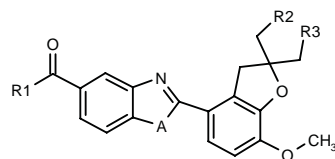
283121

2-(7-Methoxyspiro[benzofuran-2(3*H*),1'-cyclopentan]-4-yl)benzoxazole-6-carboxylic acid



C21 H19 N O5; Mol wt: 365.3831

ACTION – Bronchodilating agent, a selective inhibitor of phosphodiesterase type 4 (PDE4; $-\log IC_{50} = 8.21$). Other representative compounds within this series of benzimidazole and benzoxazole derivatives include the following:



Compound	R1	R2,R3	A	Formula
283134	OH	-(CH ₂) ₂ -	NH	C ₂₁ H ₂₀ N ₂ O ₄
283135	NH ₂	-(CH ₂) ₂ -	NH	C ₂₁ H ₂₁ N ₃ O ₃
283136	OH	-(CH ₂) ₂ -	O	C ₂₁ H ₁₉ NO ₅
283137	OH	-CH ₂ OCH ₂ -	O	C ₂₁ H ₁₉ NO ₆

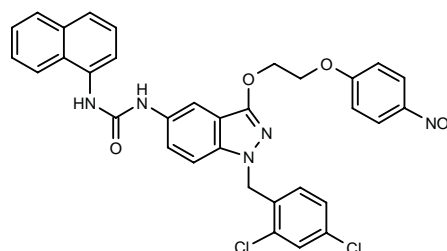
SOURCE – Byk Gulden.

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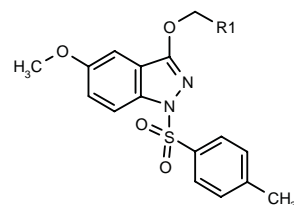
283191

N-[1-(2,4-Dichlorobenzyl)-3-[2-(4-nitrophenoxy)ethoxy]-1*H*-indazol-5-yl]-*N'*-(naphthalen-1-yl)urea

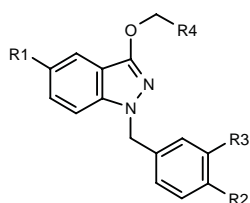


C33 H25 Cl₂ N₅ O₅; Mol wt: 642.4965

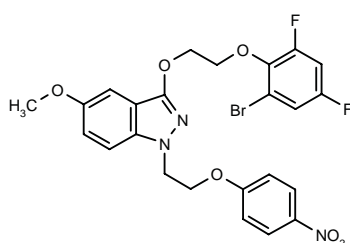
ACTION – Antiasthmatic, antiallergic, antiinflammatory, immunomodulating and neuroprotective agent, an inhibitor of peptidylprolyl isomerase (PPIase or rotamase) activity (100% inhibition at 10 μ M). *In vivo*, compound was shown to inhibit ovalbumin-induced late-phase eosinophilia in sensitized guinea pigs, giving 58% inhibition at 10 mg/kg i.p. given at 2 h before challenge. Other specifically claimed compounds from this series of 1,5- and 3-*O*-substituted 1*H*-indazole derivatives include the following:



Compound	R1	Formula
283192	5-(3-CF ₃ -Ph)-1,2,4-oxadiazol-3-yl	C ₂₅ H ₁₉ F ₃ N ₄ O ₅ S
283193	2-Br-4,6-(MeO) ₂ -PhOCH ₂	C ₂₃ H ₁₉ BrF ₂ N ₂ O ₅ S
283194	2-oxo-1,2,3,4-tetrahydro-6-quinolinyl-CO	C ₂₆ H ₂₃ N ₃ O ₆ S
283195	2,4-(F) ₂ -PhNHCO	C ₂₃ H ₁₉ F ₂ N ₃ O ₅ S



Compound	R1	R2	R3	R4	Formula
283196	OMe	H	NO ₂	6-Cl-1,3-benzodioxol-5-yl	C ₂₃ H ₁₈ ClN ₃ O ₆
283197	NO ₂	H	NO ₂	4-F-PhCH ₂ CH ₂	C ₂₃ H ₁₉ FN ₃ O ₅
283198	OMe	H	NH ₂	6-Cl-1,3-benzodioxol-5-yl	C ₂₃ H ₂₀ ClN ₃ O ₄
283199	OMe	F	H	4-NO ₂ -PhOCH ₂	C ₂₃ H ₂₀ FN ₃ O ₅
283201	SMe	Cl	Cl	2-Br-4,6-(F) ₂ -PhOCH ₂	C ₂₃ H ₁₇ BrCl ₂ F ₂ N ₂ O ₂ S



283200: C₂₄ H₂₀ Br F₂ N₃ O₆

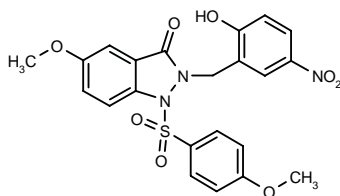
SOURCE – Arzneimittelwerk Dresden.

REFERENCES

1. Schindler, R. et al. (Arzneimittelwerk Dresden GmbH) *Novel 1,5 and 3-O-substd. 1H-indazoles with anti-asthmatic, anti-allergic, anti-inflammatory, immuno-modulating and neuro-protective effect, method for the production and use thereof as medicaments.* DE 19821002, WO 9958503.

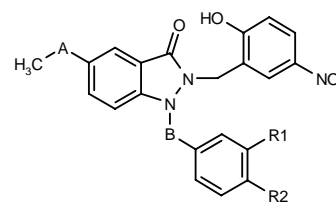
283202

2-(2-Hydroxy-5-nitrobenzyl)-5-methoxy-1-(4-methoxyphenylsulfonyl)-2,3-dihydro-1H-indazol-3-one



C₂₂ H₁₉ N₃ O₈ S; Mol wt: 485.4711

ACTION – Antiasthmatic, antiallergic, antiinflammatory, immunomodulating and neuroprotective agent, an inhibitor of peptidylprolyl isomerase (PPIase or rotamase) activity (70% inhibition at 10 μM). *In vivo*, compound was shown to inhibit ovalbumin-induced late-phase eosinophilia in sensitized guinea pigs, affording 97% inhibition at 30 mg/kg i.p. given at 2 h before and 4 h after challenge. Other compounds from this series of 1,2,5-trisubstituted 1,2-dihydroindazol-3-one derivatives include the following:



Compound	R1	R2	A	B	Formula
283203	H	Me	O	SO ₂	C ₂₂ H ₁₉ N ₃ O ₇ S
283205	H	OCF ₃	O	SO ₂	C ₂₂ H ₁₆ F ₃ N ₃ O ₈ S
283206	H	Cl	O	SO ₂	C ₂₁ H ₁₆ ClN ₃ O ₇ S
283207	H	F	O	SO ₂	C ₂₁ H ₁₆ FN ₃ O ₇ S
283208	Cl	Cl	S	CH ₂	C ₂₂ H ₁₇ Cl ₂ N ₃ O ₄ S

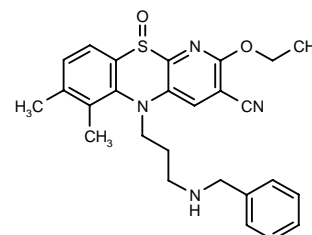
SOURCE – Arzneimittelwerk Dresden.

REFERENCES

1. Schindler, R. et al. (Arzneimittelwerk Dresden GmbH) *Novel 1,2,5-trisubstd. 1,2-dihydro-indazol-3-ones with anti-asthmatic, anti-allergic, anti-inflammatory, immuno-modulating and neuro-protective effect, method for the production and use thereof as a medicament.* DE 19821003, WO 9958504.

283402

5-[3-(Benzylamino)propyl]-2-ethoxy-6,7-dimethyl-10-oxo-5H-pyrido[2,3-b][1,4]benzothiazine-3-carbonitrile



C₂₆ H₂₈ N₄ O₂ S; Mol wt: 460.5992

ACTION – Antiasthmatic and antiallergic agent that acts by inhibiting the release of chemical mediators such as 5-HT, histamine and leukotrienes. Compound inhibited 5-HT release from rat RBL-2H3 cells with an IC₅₀ value of 4 μM, as well as histamine and leukotriene release from human basophils (IC₅₀ = 10-30 and 3 μM, respectively). *In vivo*, it proved effective in a DNP/bovine serum albumin (BSA)-induced allergic reaction model in rats, inhibiting histamine and leukotriene release by 60 and 70%, respectively, at 10 mg/kg p.o. given 30 min prior to DNP-BSA injection.

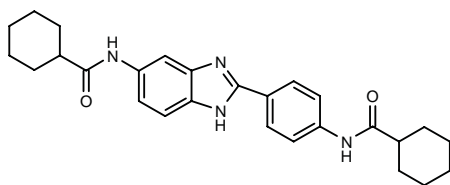
SOURCE – Eisai.

REFERENCES

1. Yamada, K. et al. (Eisai Co., Ltd.) *Heterocycle-fused benzothiazine derivs.* WO 9943683.

283748

N-[2-[4-(Cyclohexylcarboxamido)phenyl]-1*H*-benzimidazol-5-yl]cyclohexanecarboxamide



C27 H32 N4 O2; Mol wt: 444.5758

ACTION – Small-molecule inhibitor of IgE responses proven active *ex vivo* and *in vivo*. In an *ex vivo* assay in which antibody responses to antigen priming in mice were assessed, IC₅₀ values ranged from 100 pM to 1 nM, and in an *in vivo* assay in which the IgE response in irradiated mice subsequently sensitized with antigen was evaluated, the 50% inhibitory dose ranged from 100 µg/kg/day to 10 mg/kg/day. Potentially useful in the treatment of allergies and/or asthma or any other condition associated with excess IgE levels.

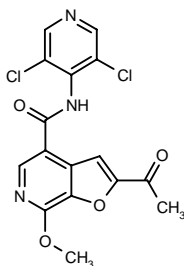
SOURCE – Avanir.

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1. Sircar, J. et al. (Avanir Pharmaceuticals) *Benzimidazole analogs as down-regulators of IgE*. WO 9961013, WO 9961019, WO 9961020.

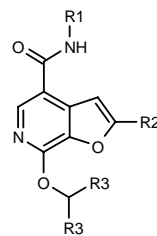
284620

2-Acetyl-*N*-(3,5-dichloropyridin-4-yl)-7-methoxyfuro-[2,3-*c*]pyridine-4-carboxamide



C16 H11 Cl2 N3 O4; Mol wt: 380.1859

ACTION – An inhibitor of phosphodiesterase type 4 (PDE4) and the production of TNF, with potential in the treatment of a broad range of disorders including asthma, chronic obstructive pulmonary disease, chronic bronchitis, atopic dermatitis, allergic rhinitis, atopic eczema, rheumatoid arthritis, joint inflammation, ulcerative colitis and Crohn's disease. Other specifically claimed compounds within this series of furopyridine derivatives include the following:



Compound	R1	R2	R3	Formula
284621	3-Me-1-oxido-4-Pyr	Ac	H	C ₁₇ H ₁₉ N ₃ O ₅
284622	3-Cl-4-Pyr	Et	H	C ₁₆ H ₁₄ ClN ₃ O ₃
284623	3,5-(Cl)2-1-oxido-4-Pyr	Et	H	C ₁₆ H ₁₃ Cl ₂ N ₃ O ₄
284624	3,5-(Cl)2-4-Pyr	4-THP	H	C ₁₉ H ₁₇ Cl ₂ N ₃ O ₄
284625	3,5-(Cl)2-1-oxido-4-Pyr	3-Pyr	H	C ₁₉ H ₁₂ Cl ₂ N ₄ O ₄
284626	4-CN-1-Me-5-pyrazolyl	Et	F	C ₁₆ H ₁₃ F ₂ N ₅ O ₃

SOURCE – Darwin Discovery.

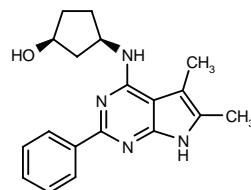
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1. Dyke, H.J. et al. (Darwin Discovery Ltd.) *Furopyridine derivs. and their therapeutic use*. WO 9964423.

CDS-90910

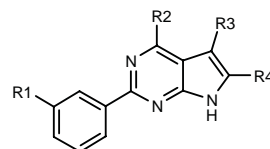
284386

cis-3-(5,6-Dimethyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylamino)cyclopentanol



C19 H22 N4 O; Mol wt: 322.4098

ACTION – Agent for the treatment of asthma, bronchitis, allergic rhinitis, chronic obstructive pulmonary disease, renal disorders, gastrointestinal disorders and ocular disorders, an adenosine receptor antagonist with selectivity for A₃ receptors (K_i = 1.0 nM) relative to A₁, A_{2a} and A_{2b} receptors (K_i = 180, 230 and 670 nM, respectively). Other specifically claimed compounds within this series of pyrrolo[2,3-*d*]pyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
284388	H	NHCH2CH2NHAc	H	CH2OPh	C ₂₃ H ₂₃ N ₅ O ₂
284389	H	3-(AcNH)-1-Pip	Me	Me	C ₂₁ H ₂₅ N ₅ O
284390	Cl	trans-4-OH-1-cyclohexyl-NH	H	H	C ₁₈ H ₁₉ ClN ₄ O
284392	H	NHCH2CH2NHAc	Me	4-F-PhOCH2	C ₂₄ H ₂₄ FN ₅ O ₂
284393	H	NHCH2CH2NHCONHMe	Me	CH2OPh	C ₂₄ H ₂₆ N ₆ O ₂

SOURCE – Cadus.

REFERENCES

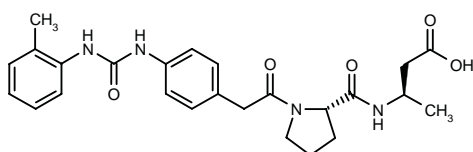
1. Castelhana, A.L. et al. (Cadus Pharmaceutical Corp.) *Pyrolo[2,3d]pyrimidine compsns. and their use*. WO 9962518.

oMePUPA-V

283894

3(R)-[1-[2-[4-[3-(2-Methylphenyl)ureido]phenyl]acetyl]-pyrrolidin-2(S)-ylcarboxamido]butyric acid

3(R)-[1-[2-[4-[3-(2-Methylphenyl)ureido]phenyl]acetyl]-L-prolylamino]butyric acid



C25 H30 N4 O5; Mol wt: 466.5350

ACTION – Cell adhesion inhibitor that is particularly well suited for the treatment of inflammatory and autoimmune diseases. The compound specifically inhibits VLA-4 binding to its ligands, i.e., VCAM-1 and fibronectin, with no measurable activity against $\alpha_4\beta_7$, VLA-5 or gpIIb/IIIa. In *Ascaris suum*-sensitive sheep, treatment with aerosolized oMePUPA-V at doses of 0.1, 1 and 3 mg prior to allergen challenge inhibited both the early and late airways responses and the hyperresponsiveness to carbachol, while being devoid of irritant effect; the effective dose of the compound could be reduced (0.03 mg) with multiple treatments. oMePUPA-V was also effective in a murine model of contact hypersensitivity. Potentially useful in the treatment of asthma, multiple sclerosis and inflammatory bowel disorders.

SOURCE – Biogen.

REFERENCES

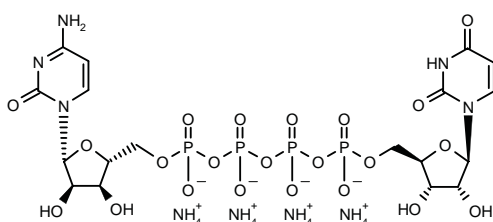
1. Lee, W.-C. and Gill, A. (Biogen, Inc.) *A novel VLA-4 inhibitor: oMePUPA-V*. WO 9961421.

TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES (COPD)

283747

P¹-(Cytidin-5'-yl)-P⁴-(uridin-5'-yl)tetraphosphate tetra-ammonium salt

CP₄U



C18 H23 N5 O22 P4 . 4 H4 N; Mol wt: 857.4431

ACTION – Highly stable and selective agonist of P2Y₂ and P2Y₄ purinoceptors with EC₅₀ values for activation of P2Y₂ and P2Y₄ receptors of 0.45 and 0.65 μ mol, respectively, whereas the EC₅₀ value for P2Y₆ receptors was 3.5 μ mol and no activity was detected at P2Y₁ receptors. The compound also potentially increased chloride secretion in human nasal airways epithelial cells and thereby enhanced the clearance of mucus by increasing the hydration of retained mucus secretions, stimulating the production of mucins and increasing ciliary beat frequency. Potentially useful in the treatment of chronic obstructive pulmonary diseases (COPD) such as chronic bronchitis and cystic fibrosis, as well as in immobilized patients at risk for developing pneumonia and in the treatment of sinusitis and otitis media.

SOURCES – Inspire Pharmaceuticals; University of North Carolina, Chapel Hill, NC (US).

REFERENCES

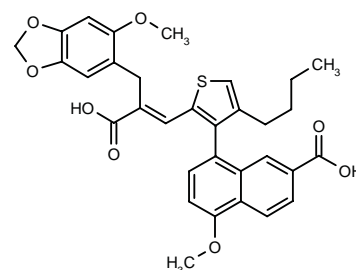
1. Yerxa, B.R. et al. (Inspire Pharmaceuticals, Inc.; University of North Carolina) *Therapeutic dinucleotide and derivs*. WO 9961012.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

282158

8-[4-Butyl-2-[2-carboxy-3-(6-methoxy-1,3-benzodioxol-5-yl)-1(E)-propenyl]-3-thienyl]-5-methoxy-2-naphthyl-carboxylic acid



C32 H30 O8 S; Mol wt: 574.6470

ACTION – Endothelin receptor antagonist with potential in the treatment of cardiovascular and renal diseases such as hypertension, acute and chronic renal failure, ciclosporin-induced nephrotoxicity, benign prostatic hypertrophy, pulmonary hypertension, migraine, stroke, cerebrovascular vasospasm, myocardial ischemia, angina, heart failure, atherosclerosis, and as an adjunct in angioplasty for the prevention of restenosis.

SOURCE – SmithKline Beecham.

REFERENCES

1. Elliott, J.D. (SmithKline Beecham Corp.) *Endothelin receptor antagonists*. US 5968971, WO 9728159.

SOURCE – Cadus.

REFERENCES

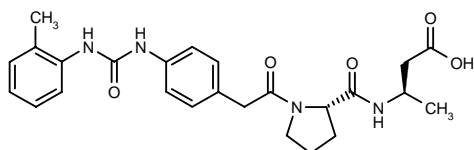
1. Castelhana, A.L. et al. (Cadus Pharmaceutical Corp.) *Pyrrolo[2,3d]pyrimidine compsns. and their use*. WO 9962518.

oMePUPA-V

283894

3(R)-[1-[2-[4-[3-(2-Methylphenyl)ureido]phenyl]acetyl]-pyrrolidin-2(S)-ylcarboxamido]butyric acid

3(R)-[1-[2-[4-[3-(2-Methylphenyl)ureido]phenyl]acetyl]-L-prolylamino]butyric acid



C25 H30 N4 O5; Mol wt: 466.5350

ACTION – Cell adhesion inhibitor that is particularly well suited for the treatment of inflammatory and autoimmune diseases. The compound specifically inhibits VLA-4 binding to its ligands, i.e., VCAM-1 and fibronectin, with no measurable activity against $\alpha_4\beta_7$, VLA-5 or gp11b/IIIa. In *Ascaris suum*-sensitive sheep, treatment with aerosolized oMePUPA-V at doses of 0.1, 1 and 3 mg prior to allergen challenge inhibited both the early and late airways responses and the hyperresponsiveness to carbachol, while being devoid of irritant effect; the effective dose of the compound could be reduced (0.03 mg) with multiple treatments. oMePUPA-V was also effective in a murine model of contact hypersensitivity. Potentially useful in the treatment of asthma, multiple sclerosis and inflammatory bowel disorders.

SOURCE – Biogen.

REFERENCES

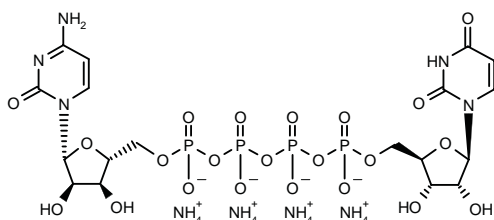
1. Lee, W.-C. and Gill, A. (Biogen, Inc.) *A novel VLA-4 inhibitor: oMePUPA-V*. WO 9961421.

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283747

P¹-(Cytidin-5'-yl)-P⁴-(uridin-5'-yl)tetraphosphate tetra-ammonium salt

CP₄U



C18 H23 N5 O22 P4 . 4 H4 N; Mol wt: 857.4431

ACTION – Highly stable and selective agonist of P2Y₂ and P2Y₄ purinoceptors with EC₅₀ values for activation of P2Y₂ and P2Y₄ receptors of 0.45 and 0.65 μ mol, respectively, whereas the EC₅₀ value for P2Y₆ receptors was 3.5 μ mol and no activity was detected at P2Y₁ receptors. The compound also potentially increased chloride secretion in human nasal airways epithelial cells and thereby enhanced the clearance of mucus by increasing the hydration of retained mucus secretions, stimulating the production of mucins and increasing ciliary beat frequency. Potentially useful in the treatment of chronic obstructive pulmonary diseases (COPD) such as chronic bronchitis and cystic fibrosis, as well as in immobilized patients at risk for developing pneumonia and in the treatment of sinusitis and otitis media.

SOURCES – Inspire Pharmaceuticals; University of North Carolina, Chapel Hill, NC (US).

REFERENCES

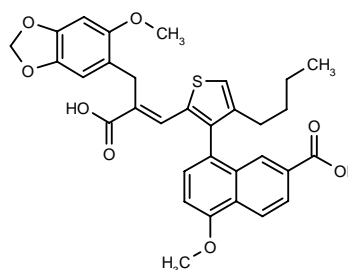
1. Yerxa, B.R. et al. (Inspire Pharmaceuticals, Inc.;University of North Carolina) *Therapeutic dinucleotide and derivs*. WO 9961012.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

282158

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C32 H30 O8 S; Mol wt: 574.6470

ACTION – Endothelin receptor antagonist with potential in the treatment of cardiovascular and renal diseases such as hypertension, acute and chronic renal failure, ciclosporin-induced nephrotoxicity, benign prostatic hypertrophy, pulmonary hypertension, migraine, stroke, cerebrovascular vasospasm, myocardial ischemia, angina, heart failure, atherosclerosis, and as an adjunct in angioplasty for the prevention of restenosis.

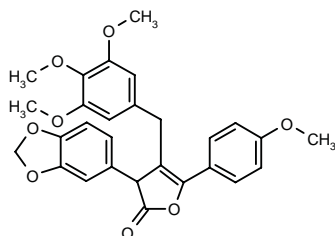
SOURCE – SmithKline Beecham.

REFERENCES

1. Elliott, J.D. (SmithKline Beecham Corp.) *Endothelin receptor antagonists*. US 5968971, WO 9728159.

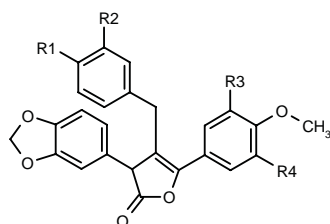
283812

3-(1,3-Benzodioxol-5-yl)-5-(4-methoxyphenyl)-4-(3,4,5-trimethoxybenzyl)furan-2(3H)-one



C28 H26 O8; Mol wt: 490.5054

ACTION – Endothelin antagonist that binds potently and selectively to ET_A receptors versus ET_B receptors (IC₅₀ = 20 nM vs. > 2500 nM). Potentially useful for treating hypertension, congestive heart failure, myocardial infarction/myocardial ischemia and pulmonary hypertension. Other exemplified furanones are:



Compound	R1	R2	R3	R4	Formula
283813	H	H	H	H	C ₂₅ H ₂₀ O ₅
283814	OMe	H	OMe	OMe	C ₂₈ H ₂₆ O ₈
283815	OMe	Me	H	H	C ₂₇ H ₂₄ O ₆

SOURCE – Warner-Lambert.

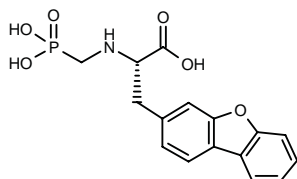
REFERENCES

- Cheng, X.-M. et al. (Warner-Lambert Co.) *Furanone endothelin antagonists*. US 5998468, WO 9708169.

CGS-35066^{1,3,4}

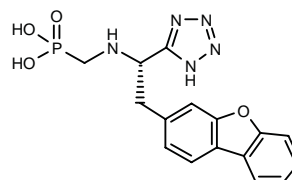
281784

3-(Dibenzo[*b,d*]furan-3-yl)-2(*S*)-(phosphonomethyl-amino)propionic acid



C16 H16 N O6 P; Mol wt: 349.2774

ACTION – Potent and selective inhibitor of human endothelin-converting enzyme-1 (ECE-1; IC₅₀ = 22 nM) with significantly less neutral endopeptidase (NEP)-inhibitory activity (IC₅₀ = 2.3 μM). Compound also showed ECE inhibitory activity *in vivo*, blocking big ET-1-induced increases in mean arterial pressure in anesthetized rats (89 and 84%, respectively, at 15 and 90 min after 10 mg/kg i.v.) and in conscious rats (61-98% at 30 min and 29-84% at 120 min following 0.3-10 mg/kg i.v.). Another related compound is:



CGS-34043 [281873]¹⁻³: C16 H16 N5 O4 P

SOURCE – Novartis.

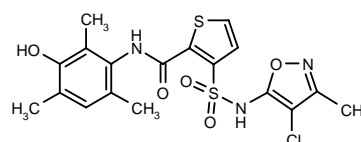
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- Trapani, A.J. et al. *Effect of CGS 35066, a potent and selective inhibitor of ECE-1 on the big ET-1-induced pressor response in the rat*. 6th Int Conf Endothelin (Oct 10-13, Montreal) 1999, Abst 015.

TBC-2576

281051

3-[*N*-(4-Chloro-3-methylisoxazol-5-yl)sulfamoyl]-*N*-(3-hydroxy-2,4,6-trimethylphenyl)thiophene-2-carboxamide



C18 H18 Cl N3 O5 S2; Mol wt: 455.9412

M.p. 75-8 °C.

ACTION – Potent and selective endothelin receptor antagonist with high affinity for ET_A (IC₅₀ = 0.19 nM) relative to ET_B receptors (ET_A/ET_B selectivity > 10,000), proven to reduce pulmonary arterial pressure by 90-100% at 5 mg/kg p.o. in a model of acute hypoxia-induced pulmonary hypertension in rats. Compound showed a good oral pharmacokinetic profile, with a serum half-life of 7.3 h in rats, as well as excellent aqueous solubility. Potentially useful for the treatment of hypertension, congestive heart failure, renal failure, cerebral vasospasm, myocardial infarction and pulmonary disorders.

SOURCE – Texas Biotechnology.

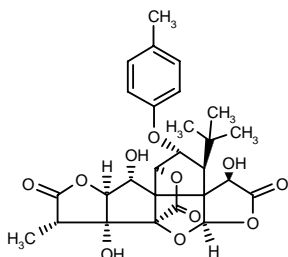
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- Wu, C. et al. *Endothelin antagonists: Substituted mesitylcarboxamides with high potency and selectivity for ETA receptors*. J Med Chem 1999, 42(22): 4485.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

282153

(1*S*,2*R*,3*S*,4*R*,6*aR*,7*aR*,7*bR*,8*S*,10*aS*,11*R*)-3-*tert*-Butyl-2-(4-methylphenoxy)-4,7*b*,11-trihydroxy-8-methyl-2,3,4,5,7*b*,8,10*a*,11-octahydro-9*H*-1,7*a*-(epoxymethano)-1*H*,6*aH*-cyclopenta[*c*]furo[2,3-*b*]furo[3',2':3,4]cyclopenta[1,2-*d*]-furan-5,9,12-trione



C27 H30 O11; Mol wt: 530.5230

ACTION – Ginkgolide derivative with cardioprotective properties, found to be significantly superior to ginkgolide B* when tested in isolated rat hearts subjected to ischemia and reperfusion, ameliorating left ventricular end-diastolic pressure during and after ischemia, and the recovery of cardiac work during reperfusion, while being devoid of hemodynamic effects.

SOURCE – CNRS.

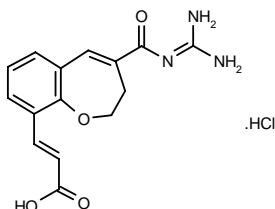
REFERENCES

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*See **BN-52021** Drug Data Rep 1986, 008(05): 0452.

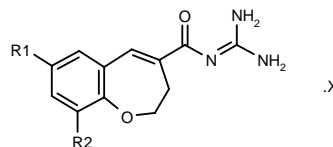
282620

3-[4-(Guanidinocarbonyl)-2,3-dihydro-1-benzoxepin-9-yl]prop-2(*E*)-enoic acid hydrochloride



C15 H15 N3 O4 . HCl; Mol wt: 337.7614

ACTION – An inhibitor of Na⁺/H⁺ exchange (IC₅₀ < 0.1 μM in rat thymus cells) with potential in the treatment of cardiovascular, cerebrovascular and renal diseases, atherosclerosis and shock. A representative compound from a series of guanidine derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
282621	H	SO ₂ Me	HCl	C ₁₃ H ₁₅ N ₃ O ₄ S.HCl
282622	Cl	SO ₂ Me		C ₁₃ H ₁₄ ClN ₃ O ₄ S
282623	H	CONHC(=NH)NH ₂	2HCl	C ₁₄ H ₁₆ N ₆ O ₃ .2HCl

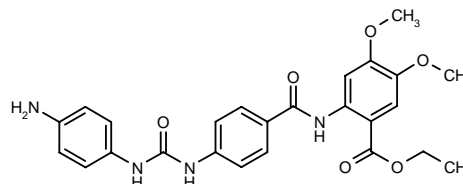
SOURCE – Fujisawa.

REFERENCES

1. Takenaka, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Guanidine derivs.* WO 9955690.

282968

2-[4-[3-(4-Aminophenyl)ureido]benzamido]-4,5-dimethoxybenzoic acid ethyl ester



C25 H26 N4 O6; Mol wt: 478.5024

ACTION – Agent for the prevention of restenosis following percutaneous transluminal coronary angioplasty (PTCA), a urea derivative of tranilast with potent inhibitory activity against platelet-derived growth factor (PDGF)-induced vascular smooth muscle cell proliferation (IC₅₀ = 0.08 μM), exhibiting at least 250-fold greater potency than tranilast (IC₅₀ = 19.8 μM).

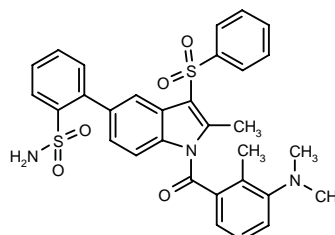
SOURCE – Japan Energy.

REFERENCES

1. Ogita, H. et al. *Synthesis and structure-activity relationship of inhibitor on smooth muscle cell proliferation induced by PDGF*. 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 1P-03.

282970

2-[1-[3-(Dimethylamino)-2-methylbenzoyl]-2-methyl-3-(phenylsulfonyl)-1*H*-indol-5-yl]benzenesulfonamide



C31 H29 N3 O5 S2; Mol wt: 587.7181

ACTION – Potent and selective chymase inhibitor (IC_{50} = 32 nM) with 1260-fold selectivity over the closely related serine protease α -chymotrypsin, potentially useful for preventing tissue remodeling in cardiovascular diseases.

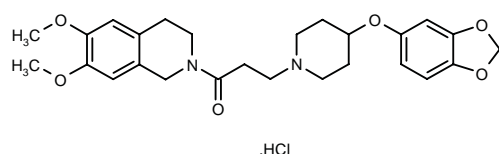
SOURCE – Wakunaga.

REFERENCES

1. Nishimura, K. et al. *Studies on selective chymase inhibitors*. 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 1P-04.

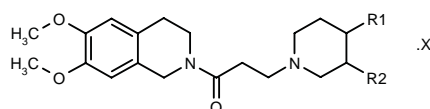
283441

3-[4-(1,3-Benzodioxol-5-yloxy)piperidin-1-yl]-1-[6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]propan-1-one hydrochloride



C26 H32 N2 O6 . HCl; Mol wt: 505.0077

ACTION – Agent for the treatment of cardiovascular disorders such as angina pectoris, myocardial infarction, congestive heart failure and arrhythmia that acts as an I_f current inhibitor and bradycardic agent. Other compounds from this series of 2-(1-piperidylalkanoyl)-1,2,3,4-tetrahydroisoquinoline derivatives include the following:



Compound	R1	R2	X	Formula
283443	3,4-(MeO)2-PhNH	H	2HCl	C ₂₇ H ₃₇ N ₃ O ₅ ·2HCl
283444	H	4-EtO-3-MeO-PhOCH2		C ₂₉ H ₄₀ N ₂ O ₆

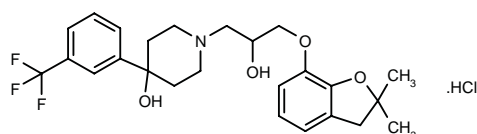
SOURCE – Yamanouchi.

REFERENCES

1. Watanabe, T. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *2-(1-Piperidylalkanoyl)-1,2,3,4-tetrahydroisoquinoline derivs. or their salts*. JP 1999269172.

284145

1-[3-(2,2-Dimethyl-2,3-dihydro-1-benzofuran-7-yloxy)-2-hydroxypropyl]-4-[3-(trifluoromethyl)phenyl]-4-piperidinol hydrochloride



C25 H30 F3 N O4 . HCl; Mol wt: 501.9699

ACTION – Cardioprotective agent, as demonstrated in isolated perfused rat hearts subjected to global ischemia by its ability to prolong the time to contracture (TTC); when tested at 1 μ M it produced a 90% change in TTC, as

compared to a 20% change for lemakalim at the same concentration. Compound was also shown to exhibit high affinity for the 5-HT_{1A} receptor in a binding assay (K_i = 20 nM against [³H]-8-OH-DPAT binding in rat frontal cortex membranes).

Other compounds within the scope of the patent are reported to be mainly useful as anxiolytic agents*.

SOURCE – Egis.

REFERENCES

1. Ágal, B. et al. (Egis Pharmaceuticals Ltd.) *Benzofuran derivs., pharmaceutical compns. containing the same, and a process for the preparation of the active ingredient*. WO 9958527.

*See 284146 under ANXIOLYTICS.

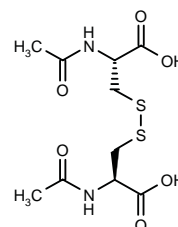
H-327/86

259644

N,N'-Diacetyl-L-cystine

D-7042

D-7193 (as di-L-lysine salt)



C10 H16 N2 O6 S2; Mol wt: 324.3764

ACTION – Immunomodulator, the disulfide dimer of *N*-acetyl-L-cysteine proven to stimulate delayed-type hypersensitivity reactions (contact hypersensitivity) induced by fluorescein isothiocyanate (Th2-type reaction) or oxazolone, but to reduce the reaction to DNFB (Th1-type reaction) in mice, with maximal effect at 3 μ mol/kg/day for 6 days. In LDL receptor-deficient 10-week-old rabbits, compound given at 3 μ mol/kg/day p.o. for 12 weeks significantly decreased atherosclerotic lesions measured as intima/media ratio in the thoracic aorta, without affecting plasma lipids. In severe atherosclerotic, 40-week-old rats, it was able to improve endothelium-mediated vascular relaxation. Currently undergoing phase II clinical studies to evaluate its effect on both endothelium-mediated vascular relaxation in hypercholesterolemic patients and on ischemic episodes in patients with stable angina pectoris. Potentially useful for the treatment of atherosclerosis.

SOURCE – AstraZeneca.

REFERENCES

1. Andersson, C.-M.A. et al. (Astra AB) *The pharmacological use of certain cystine derivs.* EP 463514, EP 532595, EP 727207, JP 1992230359, JP 1993507705, US 5441976, US 5780508, WO 9118594.

2. Bergstrand, H. and Rollof, J. (Astra AB) *New use of derivs. of cystine*. WO 9746229.

3. Pettersson, K. et al. *The immunomodulator H 327/86 reduces atherosclerosis development and improves endothelial vasodilatory function in WHHL rabbits*. Circulation 1999, 100(18, Suppl. 1): Abst 4386.

4. Särnstrand, B. et al. *N,N'*-Diacetyl-L-cystine-the disulfide dimer of N-acetylcysteine-is a potent modulator of contact sensitivity/delayed type hypersensitivity reactions in rodents. *J Pharmacol Exp Ther* 1999, 288(3): 1174.

5. *55 New chemical entities in the combined AstraZeneca pipeline.* DailyDrugNews.com (Daily Essentials) 1999, Jan 25.

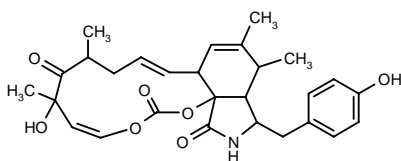
6. *AstraZeneca takes an ambitious approach to drug R&D.* DailyDrugNews.com (Daily Essentials) 1999, Dec 13.

7. *Major innovations fuel R&D at Astra.* DailyDrugNews.com (Daily Essentials) 1998, Jan 28.

PHENOCHALASIN A

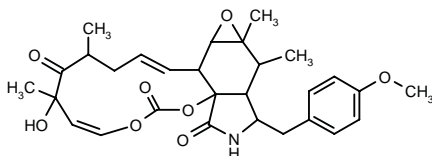
282014

(1*E*,7*Z*)-6-Hydroxy-15-(4-hydroxybenzyl)-6,8,13,14-tetramethyl-6,8,9,11a,14,14a,15,16-octahydrohexahydro-[1,3]dioxacyclotridecino[4,5-*d*]isoindole-2,7,17-trione



C₂₈ H₃₃ N O₇; Mol wt: 495.5687

ACTION – Inhibitor of lipid droplet formation in mouse peritoneal macrophages isolated from the culture broth of the fungal strain *Phomopsis* sp. FT-0211. Compound induced a concentration-dependent (6 and 20 μM) reduction in the size and number of lipid droplets in macrophages, with no cytotoxic effect at up to 20 μM. Potentially useful for delaying the progression of atherosclerosis. Another structurally related compound, which inhibited lipid droplet formation but was associated with severe cytotoxicity, is:



Phenochalasin B [282015]: C₂₉ H₃₅ N O₈

SOURCE – Kitasato Institute, Tokyo (JP).

REFERENCES

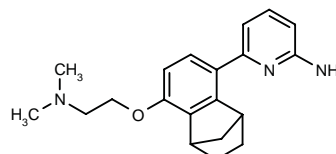
- Namatame, I. et al. *Effect of fungal metabolites cytochalasins on lipid droplet formation in mouse macrophages.* *J Antibiot* 2000, 53(1): 19.
- Tomoda, H. et al. *Phenochalasins, inhibitors of phenyl droplet formation in mouse macrophages, produced by Phomopsis sp. FT-0211.* *J Antibiot* 1999, 52(10): 851.
- Tomoda, H. et al. *Structure elucidation of fungal phenochalasins, novel inhibitors of lipid droplet formation in mouse macrophages.* *J Antibiot* 1999, 52(10): 857.

TREATMENT OF SHOCK

284050

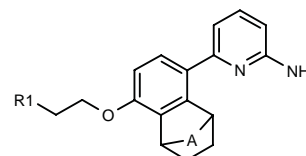
6-[8-[2-(Dimethylamino)ethoxy]-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]pyridin-2-amine

N-[2-[8-(6-Aminopyridin-2-yl)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yloxy]ethyl]-*N,N*-dimethylamine



C₂₀ H₂₅ N₃ O; Mol wt: 323.4375

ACTION – Nitric oxide synthase (NOS) inhibitor with potential in the treatment or prevention of septic shock, inflammation, migraine, stroke, reperfusion injury, inflammatory bowel disease, neurodegenerative diseases, rheumatoid arthritis, asthma, adult respiratory distress syndrome, psoriasis and cancer. Other specifically claimed compounds from this series of 2-aminopyridine derivatives include the following:



Compound	R1	A	Formula
284051	1-pyrrolidinyl	-(CH ₂) ₂ -	C ₂₂ H ₂₇ N ₃ O
284052	N(Me) ₂	-(CH ₂) ₂ -	C ₂₁ H ₂₇ N ₃ O
284053	1-pyrrolidinyl	-(CH ₂) ₂ -	C ₂₃ H ₂₉ N ₃ O
284054	4-Me-1-Piz	-(CH ₂) ₂ -	C ₂₄ H ₃₂ N ₄ O
284055	4-(PhCH ₂ CH ₂)-1-Piz	-(CH ₂) ₂ -	C ₃₁ H ₃₈ N ₄ O

SOURCE – Pfizer.

REFERENCES

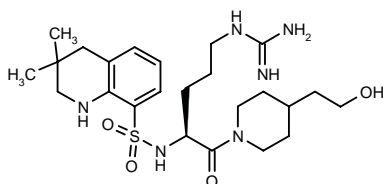
- Lowe, J.A. III (Pfizer Products Inc.) *2-Aminopyridines containing fused ring substituents as nitric oxide synthase inhibitors.* WO 9962883.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

282180

N-[4-Guanidino-1-(*S*)-[4-(2-hydroxyethyl)piperidin-1-ylcarbonyl]butyl]-3,3-dimethyl-1,2,3,4-tetrahydroquinoline-8-sulfonamide



C₂₄H₄₀N₆O₄S; Mol wt: 508.6840

ACTION – Antithrombotic agent, a thrombin inhibitor (K_i = 48 and 32 nM, respectively, against bovine and human thrombin) with improved *in vitro* potency over the parent compound argatroban (K_i = 61 and 85 nM, respectively) and highly selective over plasmin, trypsin and chymotrypsin (K_i = 210, 7.1 and > 83 μ M, respectively). It increased the activated partial thromboplastin time (aPTT) in human plasma with an IC_{200} of 1.9 μ M. In animal models of venous and arterial thrombosis, compound produced dose-dependent inhibition of thrombus formation (0.1-3 mg/kg i.v. or 1-6 mg/kg s.c.).

SOURCE – Novartis.

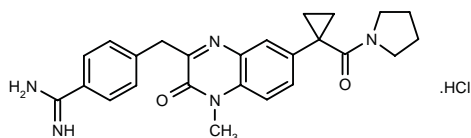
REFERENCES

1. Hoyle, W. et al. (Ciba-Geigy AG) *Trypsin and thrombin inhibitors*. EP 815103, JP 1999502219, WO 9629327.

2. Brundish, D. et al. *Design and synthesis of thrombin inhibitors: Analogues of MD-805 with reduced stereogenicity and improved potency*. J Med Chem 1999, 42(22): 4584.

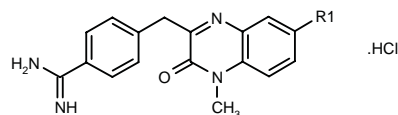
282385

4-[4-Methyl-3-oxo-7-[1-(1-pyrrolidinylcarbonyl)cyclopropyl]-3,4-dihydroquinoxalin-2-ylmethyl]benzamidinium hydrochloride

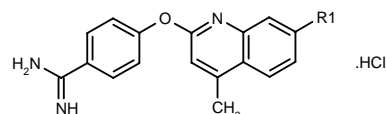


C₂₅H₂₇N₅O₂ . HCl; Mol wt: 465.9822

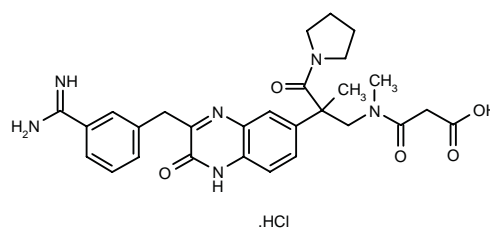
ACTION – Anticoagulant and antithrombotic agent shown to prolong the activated partial thromboplastin time (aPTT) in human plasma with an ED_{200} value (concentration doubling aPTT) of 0.095 μ M. Other specifically claimed bicyclic compounds with thrombin- and/or factor Xa-inhibitory activity include the following:



Compound	R1	Formula
282386	1-[cyclopentyl-N(COCH ₂ CO ₂ H)]-1-cyclopropyl	C ₂₈ H ₃₁ N ₅ O ₄ .HCl
282389	1-pyrrolidinyl-COC(Me) ₂	C ₂₅ H ₂₉ N ₅ O ₂ .HCl
282390	N(8-quinoliny-SO ₂)CH ₂ CO ₂ H	C ₂₈ H ₂₄ N ₆ O ₅ S.HCl



Compound	R1	Formula
282387	NHCH ₂ CH ₂ CONHCH ₂ CO ₂ H	C ₂₂ H ₂₃ N ₅ O ₄ .HCl
282388	CON(2-Pyr)CH ₂ CH ₂ CO ₂ H	C ₂₆ H ₂₃ N ₅ O ₄ .HCl



282391: C₂₈H₃₂N₆O₅ . HCl

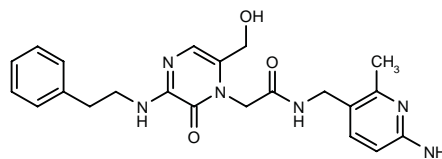
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Ries, U. et al. (Boehringer Ingelheim Pharma KG) *Bicyclic cpds. having an anti-thrombotic effect*. DE 19816983, WO 9954313.

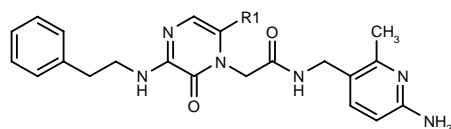
283846

N-(6-Amino-2-methylpyridin-3-ylmethyl)-2-[6-(hydroxymethyl)-2-oxo-3-(2-phenylethylamino)-1,2-dihydropyrazin-1-yl]acetamide



C₂₂H₂₆N₆O₃; Mol wt: 422.4864

ACTION – Thrombin inhibitor with selectivity for thrombin versus trypsin, potentially useful as an anticoagulant in the treatment of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation and reocclusion or restenosis of recanalized vessels. Other specifically claimed pyrazinone derivatives are:



Compound	R1	Formula
283847	CH ₂ OMe	C ₂₃ H ₂₈ N ₆ O ₃
283848	CH ₂ SMc	C ₂₃ H ₂₈ N ₆ O ₂ S
283849	CH ₂ SPh	C ₂₆ H ₃₀ N ₆ O ₂ S
283850	SOMe	C ₂₂ H ₂₆ N ₆ O ₃ S
283851	SMe	C ₂₂ H ₂₆ N ₆ O ₂ S

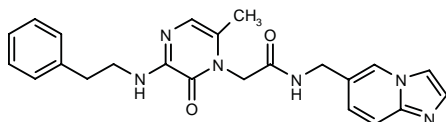
SOURCE – Merck & Co.

REFERENCES

1. Sanderson, P.E. et al. (Merck & Co., Inc.) *Pyrazinone thrombin inhibitors*. WO 9959591.

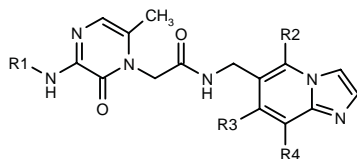
284036

N-(Imidazo[1,2-*a*]pyridin-6-ylmethyl)-2-[6-methyl-2-oxo-3-(2-phenylethylamino)-1,2-dihydropyrazin-1-yl]acetamide

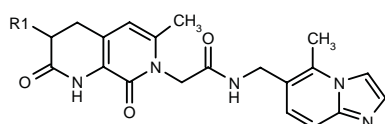


C₂₃ H₂₄ N₆ O₂; Mol wt: 416.4826

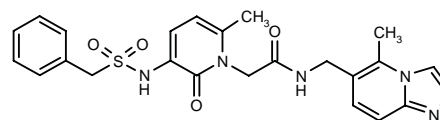
ACTION – Anticoagulant, a selective thrombin inhibitor expected to be useful for treating or preventing unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation and reocclusion or restenosis of recanalized vessels. Other specifically claimed imidazopyridine derivatives are:



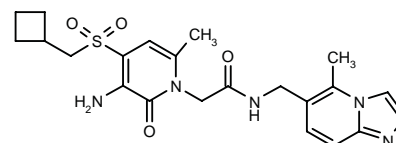
Compound	R1	R2	R3	R4	Formula
284037	CH ₂ CH ₂ Ph	Me	H	H	C ₂₄ H ₂₆ N ₆ O ₂
284038	CH ₂ CH ₂ Ph	H	H	Me	C ₂₄ H ₂₆ N ₆ O ₂
284039	CH ₂ CH ₂ Ph	H	Me	H	C ₂₄ H ₂₆ N ₆ O ₂
284040	CH ₂ CH ₂ Ph	H	H	H	C ₂₃ H ₂₄ N ₆ O ₂
284041	2-Pyr-CH ₂ CH ₂	Me	H	H	C ₂₃ H ₂₅ N ₇ O ₂



Compound	R1	Formula
284044	CH ₂ Ph	C ₂₇ H ₂₇ N ₅ O ₃
284045	CH ₂ CH[(S)-Me]Et	C ₂₅ H ₃₁ N ₅ O ₃



284042: C₂₄ H₂₅ N₅ O₄ S



284043: C₂₂ H₂₇ N₅ O₄ S

SOURCE – Merck & Co.

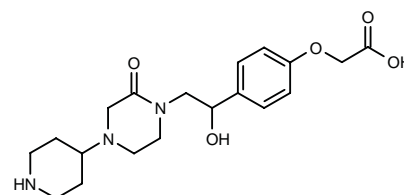
REFERENCES

1. Sanderson, P.E. and Naylor-Olsen, A.M. (Merck & Co., Inc.) *Imidazopyridine thrombin inhibitors*. WO 9961442.

ANTIPLATELET THERAPY

282833

2-[4-[1-Hydroxy-2-[2-oxo-4-(4-piperidinyl)piperazin-1-yl]ethyl]phenoxy]acetic acid



C₁₉ H₂₇ N₃ O₅; Mol wt: 377.4383

ACTION – Antiplatelet agent, a representative compound from a series of benzyl alcohol derivatives that potently inhibits ADP-induced human platelet aggregation (IC₅₀ = 0.24 μM).

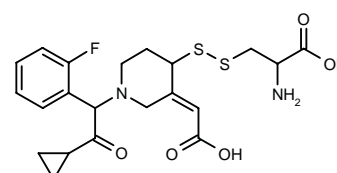
SOURCE – Meiji Seika.

REFERENCES

1. Kobayashi, K. et al. (Meiji Seika Kaisha, Ltd.) *Benzylalcohol derivs. having platelet aggregation inhibitory effect*. JP 1999279174.

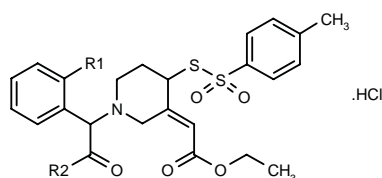
283396

2-Amino-3-[3-(carboxymethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidin-4-yl]disulfanyl]propionic acid



C₂₁ H₂₅ F N₂ O₅ S₂; Mol wt: 468.5675

ACTION – Platelet aggregation inhibitor with potent *ex vivo* inhibitory effects against ADP-induced platelet aggregation in rats (89.2% inhibition at 10 mg/kg i.v.). Within this series of cyclic amino derivatives, the following compounds are also included:



Compound	R1	R2	Formula
283397	F	cyclopropyl	C ₂₇ H ₃₀ FN ₂ O ₅ S ₂ .HCl
283399	Cl	OMe	C ₂₈ H ₂₈ ClN ₂ O ₅ S ₂ .HCl

SOURCES – Sankyo; Ube.

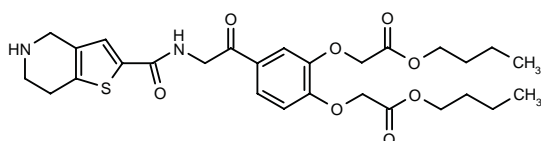
REFERENCES

1. Asai, F. et al. (Sankyo Co., Ltd.; Ube Industries, Ltd.) *Cyclic amino cpds.* WO 9943648.

ME-3229

248771

2,2'-[4-[2-(4,5,6,7-Tetrahydrothieno[3,2-c]pyridin-2-yl-carboxamido)acetyl]-1,2-phenylene]bis(oxy)bis(acetic acid) dibutyl ester



C₂₈ H₃₆ N₂ O₈ S; Mol wt: 560.6644

ACTION – Antithrombotic agent, an ester-type prodrug of the gpIIb/IIIa receptor antagonist ME-3277*. The prodrug showed antiplatelet activity *in vitro* (IC₅₀ = 0.68-2.7 μM against ADP-induced human, dog and guinea pig platelet aggregation) and *ex vivo* in guinea pigs and dogs. In dogs, it exhibited a long duration of action (up to 8 h), with no significant prolongation of bleeding time at doses associated with 90% inhibition of platelet aggregation. Compound (10-100 mg/kg p.o.) exhibited antithrombotic effects similar to aspirin and ticlopidine hydrochloride in various models of thrombosis in guinea pigs (arterio-venous shunt, photochemically induced thrombosis, chronic peripheral arterial occlusion).

SOURCE – Meiji Seika.

REFERENCES

1. Katano, K. et al. (Meiji Seika Kaisha, Ltd.) *Novel cpd. with platelet aggregation inhibitor activity.* JP 199520876, US 5594004, US 5698692, WO 9421599.

2. Kataha, K. et al. *Antiplatelet effect of ME3229, a novel orally active platelet GPIIb/IIIa antagonist.* Jpn J Pharmacol 1997, 73(Suppl. 1): Abst P-51.

3. Okudaira, N. et al. *Intestinal absorption of an ester-type prodrug, ME3229 - Studies on the efflux of metabolites formed in the enterocytes into the gut lumen.* Xenobiotic Metab Dispos 1999, 14(Suppl.): Abst 21S2-02.

4. Sugano, T. et al. *Antithrombotic effect of ME3229 on thrombus model in guinea pigs.* Jpn J Pharmacol 1997, 73(Suppl. 1): Abst P-52.

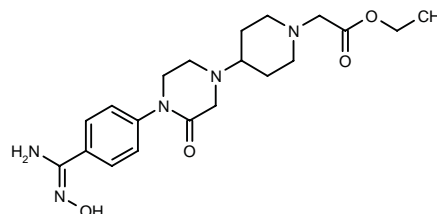
5. Meiji Seika's pipeline. DailyDrugNews.com (Daily Essentials) 1997, Feb 26.

*Drug Data Rep 1996, 018(01): 0052.

YM-68128*

259900

2-[4-[4-[4-(N-Hydroxyamidino)phenyl]-3-oxopiperazin-1-yl]piperidin-1-yl]acetic acid ethyl ester



C₂₀ H₂₉ N₅ O₄; Mol wt: 403.4801

ACTION – Orally active antiplatelet agent, a double prodrug of a monooxopiperazine derivative* that has potent *in vitro* activity against ADP- and collagen-induced platelet aggregation (IC₅₀ = 0.025 and 0.023 μM) and acts as a platelet gpIIb/IIIa receptor antagonist. The prodrug exhibited good oral bioavailability in dogs (32%) and a longer duration of antiplatelet activity than sibrifiban in cynomolgus monkeys, indicating potential for once-daily dosing.

SOURCES – Merck KGaA; Yamanouchi.

REFERENCES

1. Matsumoto, Y. et al. (Yamanouchi Pharmaceutical Co., Ltd.; Merck Patent GmbH) *Subst. amidinobenzene derivs. and medicinal compsns. thereof.* EP 905129, WO 9745413.

2. Matsumoto, Y. et al. *Novel orally active GPIIb/IIIa antagonists: Synthesis and structure-activity relationship studies of oxopiperazine derivatives.* 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 1P-02.

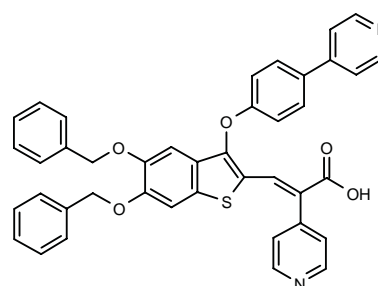
*Identified compound **259900** Drug Data Rep 1998, 020(06): 0500.

*See **241633** (see **240957**) Drug Data Rep 1997, 019(01): 0047.

THROMBOLYTICS

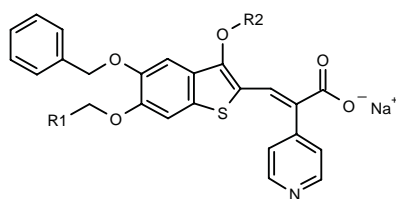
282787

3-[5,6-Bis(benzyloxy)-3-[4-(4-pyridyl)phenoxy]benzothien-2-yl]-2-(4-pyridyl)-2(E)-propenoic acid



C₄₁ H₃₀ N₂ O₅ S; Mol wt: 662.7630

ACTION – Plasminogen activator inhibitor type 1 (PAI-1) inhibitor, significantly more potent than XR-5082 as a fibrinolytic *in vitro* (IC_{50} = 2.2 μ M vs. 190 μ M). Potentially useful as a fibrinolytic and antithrombotic. Other exemplified compounds include the following:



Compound	R1	R2	Formula
282788	Ph	4-MeO-Ph	C ₃₇ H ₂₈ NNaO ₆ S
282789	Ph	4-(PhCH ₂ O)-Ph	C ₄₃ H ₃₂ NNaO ₆ S
282790	H	3-Pyr	C ₂₉ H ₂₁ N ₂ NaO ₅ S

SOURCE – ADIR.

REFERENCES

- De Nanteuil, G. et al. (ADIR et Cie.) *Benzothiophene, benzofurane and indole derivs., process for their preparation and pharmaceutical compns. containing them.* EP 955299, FR 2777886, JP 1999349586.

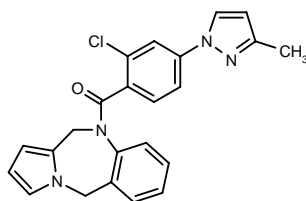
RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

VNA-932

282109

10-[2-Chloro-4-(3-methyl-1*H*-pyrazol-1-yl)benzoyl]-10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine



C23 H19 Cl N4 O; Mol wt: 402.8831

ACTION – Potent and selective, nonpeptide vasopressin V₂ receptor agonist shown to competitively inhibit [³H]-AVP binding to human V₂ receptors expressed in murine fibroblast LV2 cells with a K_i value of 39.9 nM. Compound showed full functional agonist activity, as demonstrated by the ability to stimulate cAMP formation in LV2 cells (EC₅₀ = 0.73 nM); this response was fully blocked by the V₂ receptor antagonist VPA-985. Unlike the known agonist DDAVP, no agonist activity was seen at human V_{1a}, V_{1b} or oxytocin receptors. Claimed in patent literature for the treatment of urinary incontinence, nocturnal enuresis and diabetes insipidus.

SOURCE – American Home Products.

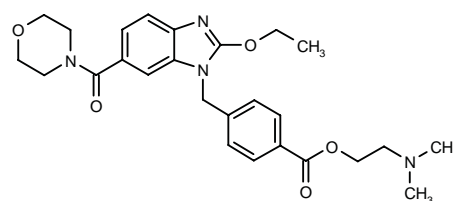
REFERENCES

- Dusza, J.P. et al. (American Home Products Corp.) *Tricyclic vasopressin agonists.* WO 9906409.
- Park, C.H. et al. *VNA-932, a nonpeptide V2 selective vasopressin agonist.* 32nd Annu Meet Am Soc Nephrol (Nov 5-8, Miami Beach) 1999, Abst A0114.

TREATMENT OF RENAL DISEASES

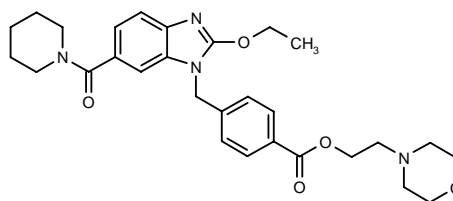
282106

4-[2-Ethoxy-6-(morpholin-4-ylcarbonyl)-1*H*-benzimidazol-1-ylmethyl]benzoic acid 2-(dimethylamino)ethyl ester



C26 H32 N4 O5; Mol wt: 480.5618

ACTION – Agent for the treatment of renal diseases, a representative compound from a series of benzimidazole derivatives reported to possess no binding affinity for angiotensin II AT₂ receptors and low affinity for AT₁ receptors, and shown to be devoid of hypotensive activity, as demonstrated in renal artery-ligated rats, in contrast to the reference compound DuP-753. In these rats, compound was more effective than DuP-753 in improving serum creatinine, BUN and creatinine clearance and in increasing survival, the mean survival time being 7.5 weeks as compared to 6 weeks for DuP-753 when both compounds were tested at 20 mg/kg/day p.o. No mortality was observed following a single administration of 500 mg/kg p.o. to mice. Another exemplified compound is:



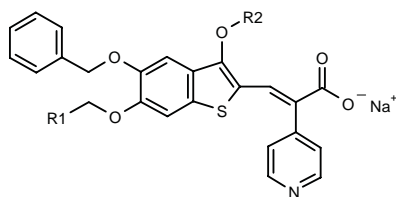
282107: C29 H36 N4 O5

SOURCE – Kureha.

REFERENCES

- Yanaka, M. et al. (Kureha Chemical Industry Co. Ltd.) *Benzimidazole deriv.* WO 9942451.

ACTION – Plasminogen activator inhibitor type 1 (PAI-1) inhibitor, significantly more potent than XR-5082 as a fibrinolytic *in vitro* ($IC_{50} = 2.2 \mu M$ vs. $190 \mu M$). Potentially useful as a fibrinolytic and antithrombotic. Other exemplified compounds include the following:



Compound	R1	R2	Formula
282788	Ph	4-MeO-Ph	C ₃₇ H ₂₈ NNaO ₆ S
282789	Ph	4-(PhCH ₂ O)-Ph	C ₄₃ H ₃₂ NNaO ₆ S
282790	H	3-Pyr	C ₂₉ H ₂₁ N ₂ NaO ₅ S

SOURCE – ADIR.

REFERENCES

1. De Nanteuil, G. et al. (ADIR et Cie.) *Benzothiophene, benzofurane and indole derivs., process for their preparation and pharmaceutical compsns. containing them.* EP 955299, FR 2777886, JP 1999349586.

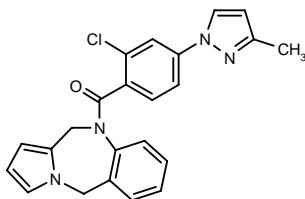
RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

VNA-932

282109

10-[2-Chloro-4-(3-methyl-1*H*-pyrazol-1-yl)benzoyl]-10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine



C₂₃ H₁₉ Cl N₄ O; Mol wt: 402.8831

ACTION – Potent and selective, nonpeptide vasopressin V₂ receptor agonist shown to competitively inhibit [³H]-AVP binding to human V₂ receptors expressed in murine fibroblast LV2 cells with a K_i value of 39.9 nM. Compound showed full functional agonist activity, as demonstrated by the ability to stimulate cAMP formation in LV2 cells (EC₅₀ = 0.73 nM); this response was fully blocked by the V₂ receptor antagonist VPA-985. Unlike the known agonist DDAVP, no agonist activity was seen at human V_{1a}, V_{1b} or oxytocin receptors. Claimed in patent literature for the treatment of urinary incontinence, nocturnal enuresis and diabetes insipidus.

SOURCE – American Home Products.

REFERENCES

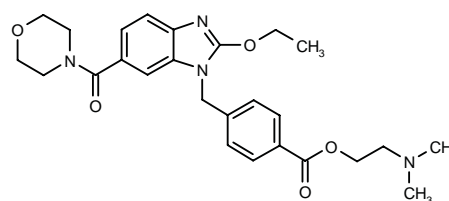
1. Dusza, J.P. et al. (American Home Products Corp.) *Tricyclic vasopressin agonists.* WO 9906409.

2. Park, C.H. et al. *VNA-932, a nonpeptide V2 selective vasopressin agonist.* 32nd Annu Meet Am Soc Nephrol (Nov 5-8, Miami Beach) 1999, Abst A0114.

TREATMENT OF RENAL DISEASES

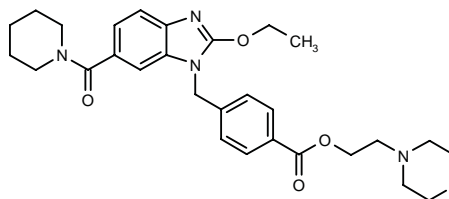
282106

4-[2-Ethoxy-6-(morpholin-4-ylcarbonyl)-1*H*-benzimidazol-1-ylmethyl]benzoic acid 2-(dimethylamino)ethyl ester



C₂₆ H₃₂ N₄ O₅; Mol wt: 480.5618

ACTION – Agent for the treatment of renal diseases, a representative compound from a series of benzimidazole derivatives reported to possess no binding affinity for angiotensin II AT₂ receptors and low affinity for AT₁ receptors, and shown to be devoid of hypotensive activity, as demonstrated in renal artery-ligated rats, in contrast to the reference compound DuP-753. In these rats, compound was more effective than DuP-753 in improving serum creatinine, BUN and creatinine clearance and in increasing survival, the mean survival time being 7.5 weeks as compared to 6 weeks for DuP-753 when both compounds were tested at 20 mg/kg/day p.o. No mortality was observed following a single administration of 500 mg/kg p.o. to mice. Another exemplified compound is:



282107: C₂₉ H₃₆ N₄ O₅

SOURCE – Kureha.

REFERENCES

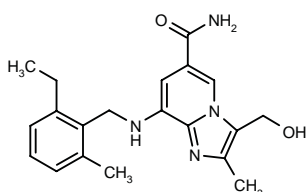
1. Yanaka, M. et al. (Kureha Chemical Industry Co. Ltd.) *Benzimidazole deriv.* WO 9942451.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

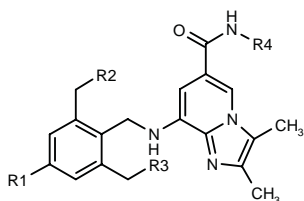
282660

8-(2-Ethyl-6-methylbenzylamino)-3-(hydroxymethyl)-2-methylimidazo[1,2-*a*]pyridine-6-carboxamide



C20 H24 N4 O2; Mol wt: 352.4356

ACTION – An inhibitor of H⁺/K⁺-ATPase that inhibits endogenously and exogenously stimulated gastric acid secretion and is potentially useful in the treatment or prevention of gastrointestinal inflammatory disorders and gastric acid-related diseases including gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome. Within this series of imidazopyridine derivatives, the following compounds are also specifically claimed:



Compound	R1	R2	R3	R4	Formula
282661	H	H	H	CH ₂ CH ₂ OH	C ₂₁ H ₂₆ N ₄ O ₂
282662	H	Me	H	H	C ₂₀ H ₂₄ N ₄ O
282663	H	Me	H	Me	C ₂₁ H ₂₆ N ₄ O
282664	H	H	H	H	C ₁₉ H ₂₂ N ₄ O
282665	F	Me	H	H	C ₂₀ H ₂₃ FN ₄ O
282666	F	H	H	H	C ₁₉ H ₂₁ FN ₄ O
282667	H	Me	Me	H	C ₂₁ H ₂₆ N ₄ O
282668	H	Me	H	CH ₂ CH ₂ OH	C ₂₂ H ₂₈ N ₄ O ₂
282669	H	Me	H	CH ₂ CH ₂ OMe	C ₂₃ H ₃₀ N ₄ O ₂

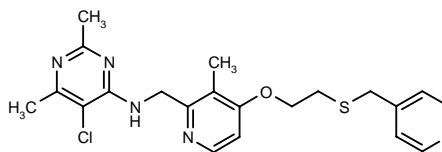
SOURCE – AstraZeneca.

REFERENCES

- Amin, K. et al. (Astra AB) *Imidazo pyridine derivs. which inhibit gastric acid secretion*. WO 9955705, WO 9955706.

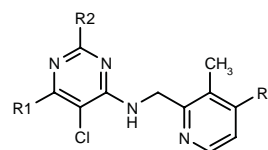
283648

N-(5-Chloro-2,6-dimethylpyrimidin-4-yl)-*N*-[3-methyl-4-[2-(4-pyridinylmethylsulfanyl)ethoxy]pyridin-2-ylmethyl]-amine



C21 H24 Cl N5 O S; Mol wt: 429.9736

ACTION – Antiulcer agent with activity against *Helicobacter pylori* (MIC₅₀ = 0.1 µg/ml or less). Other specifically claimed pyrimidin-aminomethyl-pyridine derivatives include the following:



Compound	R1=R2	R3	Formula
283649	Me	2-Me-5-NO ₂ -1-imidazolyl-CH ₂ CH ₂ SCH ₂ CH ₂ O	C ₂₁ H ₂₆ ClN ₇ O ₃ S
283650	Me	2-Me-5-NO ₂ -1-imidazolyl-CH ₂ CH ₂ S(CH ₂) ₃ O	C ₂₂ H ₂₈ ClN ₇ O ₃ S
283651	Me	4-Pyr-CH ₂ SCH ₂ CH ₂ OCH ₂ CH ₂ S	C ₂₃ H ₂₈ ClN ₅ OS ₂
283652	Me	2-Pyr-CH ₂ S(CH ₂) ₃ S	C ₂₂ H ₂₆ ClN ₅ S ₂
283653	H	2-Me-5-NO ₂ -1-imidazolyl-CH ₂ CH ₂ SCH ₂ CH ₂ O	C ₁₉ H ₂₂ ClN ₇ O ₃ S

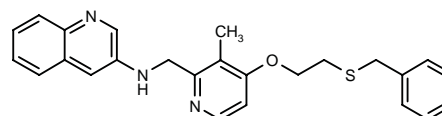
SOURCE – Byk Gulden.

REFERENCES

- Hanauer, G. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Pyrimidin-aminomethyl-pyridine derivs., their preparation and their use in the control of Helicobacter bacteria*. WO 9961439.

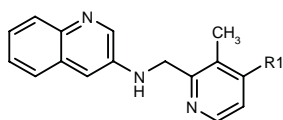
283654

N-[3-Methyl-4-[2-(4-pyridinylmethylsulfanyl)ethoxy]pyridin-2-ylmethyl]-*N*-(quinolin-3-yl)amine



C24 H24 N4 O S; Mol wt: 416.5466

ACTION – Antiulcer agent with activity against *Helicobacter pylori* (MIC₅₀ = 0.1 µg/ml or less). Other specifically claimed quinoline-aminomethyl-pyridyl derivatives include the following:



Compound	R1	Formula
283655	2-Me-5-NO ₂ -1-imidazolyl-CH ₂ CH ₂ SCH ₂ CH ₂ O	C ₂₄ H ₂₆ N ₆ O ₃ S
283656	2-Me-5-NO ₂ -1-imidazolyl-CH ₂ CH ₂ S(CH ₂) ₃ O	C ₂₅ H ₂₈ N ₆ O ₃ S
283657	2-Pyr-CH ₂ S(CH ₂) ₃ S	C ₂₅ H ₂₆ N ₄ S ₂
283658	3-Pyr-CH ₂ SCH ₂ CH ₂ O	C ₂₄ H ₂₄ N ₄ OS
283659	2-Pyr-CH ₂ SCH ₂ CH ₂ O	C ₂₄ H ₂₄ N ₄ OS

SOURCE – Byk Gulden.

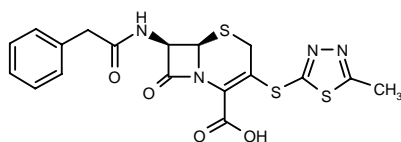
REFERENCES

1. Hanauer, G. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Quinoline-aminomethyl-pyridyl derivs. with anti-Helicobacter activity*. WO 9961438.

FR-182024

282755

(6*R*,7*R*)-3-(5-Methyl-1,3,4-thiadiazol-2-ylsulfanyl)-7-(2-phenylacetamido)-3-cephem-4-carboxylic acid



C₁₈ H₁₆ N₄ O₄ S₃; Mol wt: 448.5464

M.p. > 200 °C (*decomp.*).

ACTION – Antiulcer agent, a cephem derivative with potent *in vitro* anti-*Helicobacter pylori* activity (MIC = 0.78–6.25 ng/ml) with 10- and 50-fold greater activity than amoxicillin and clarithromycin, respectively. Compound also displayed strong activity against a clarithromycin-resistant *H. pylori* strain (MIC = 1.6 ng/ml). In a mouse infection model, it was able to eradicate *H. pylori* infection in all mice at a dose of 0.32 mg/kg p.o., whereas amoxicillin and clarithromycin were inactive or practically inactive at this dose. Even at the low dose of 0.1 mg/kg, compound eradicated *H. pylori* in 5 of 8 mice. FR-182024 has a low potential for causing diarrhea due to its low stability to hydrolysis by β-lactamases.

SOURCE – Fujisawa.

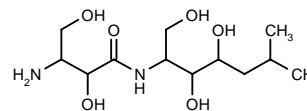
REFERENCES

1. Yoshida, Y. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Cephem cpds. and pharmaceutical use thereof*. EP 796263, JP 1998510258, WO 9617850.
2. Yoshida, Y. et al. (Fujisawa Pharmaceutical Co., Ltd.) *New cephem cpds. and pharmaceutical use thereof*. EP 882052, WO 9729111.
3. Yoshida, Y. et al. *Synthesis and anti-Helicobacter pylori activity of FR182024, a new cephem derivative*. Bioorg Med Chem Lett 1999, 9(21): 3123.

HC-74

282003

3-Amino-*N*-[2,3-dihydroxy-1-(hydroxymethyl)-5-methyl-hexyl]-2,4-dihydroxybutyramide



C₁₂ H₂₆ N₂ O₆; Mol wt: 294.3454

ACTION – Antiulcer agent isolated from a culture of *Acinetobacter* sp. HC-74 (IFO16117, FERM BP-6137) with potent antibacterial activity against *Helicobacter pylori*, as demonstrated both *in vitro* (MIC = 0.4 µg/ml against *H. pylori* strain NCTC11637) and *in vivo* in mice infected with *H. pylori* TN2F4 given a dose of 50 mg/kg b.i.d. p.o. x 2 days.

SOURCE – Takeda.

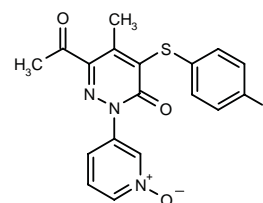
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1. Tsuboya, S. et al. (Takeda Chemical Industries, Ltd.) *Polyalcohol groups, their preparation method and use*. JP 1999222473.

INFLAMMATORY BOWEL DISEASE THERAPY

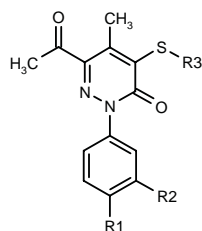
282978^{1,2}

6-Acetyl-4-(4-fluorophenylsulfanyl)-5-methyl-2-(1-oxidopyridin-3-yl)pyridazin-3(2*H*)-one



C₁₈ H₁₄ F N₃ O₃ S; Mol wt: 371.3906

ACTION – Agent for the treatment of inflammatory bowel disease, an inhibitor of cell adhesion proven to inhibit the adhesion of human neutrophils to keyhole limpet hemocyanin as a substitute for ICAM-1 (IC₅₀ = 0.98 µM). Compound was able to protect against peritonitis induced by zymosan in mice (ED₅₀ = 100 mg/kg) and to reduce neutrophil infiltration and/or accumulation at the lesion site in animals with ulcerative colitis induced by dextran sulfate or acetic acid. Additional inhibitory activity was observed against free radical production by neutrophils and increased vascular permeability. Other pyridazinone derivatives include the following:



Compound	R1	R2	R3	Formula
282980 ¹	F	H	2-thienyl	C ₁₇ H ₁₃ FN ₂ O ₂ S ₂
282981 ¹	H	Cl	Ph	C ₁₉ H ₁₅ ClN ₂ O ₂ S

SOURCE – Nihon Nohyaku.

REFERENCES

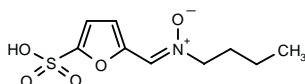
1. Gotoh, M. et al. *Synthesis and structure-activity relationships of pyridazinone derivatives possessing neutrophil adhesion inhibitory activity*. 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 1P-07.

2. Satoh, A. et al. *Pharmacological activity of pyridazinone derivatives for the treatment of ulcerative colitis*. 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 1P-08.

283860

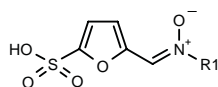
5-(*N*-Butyliminomethyl)furan-2-sulfonic acid *N*-oxide

N-Butyl-α-(5-sulfofuran-2-yl)nitron



C₉H₁₃N O₅ S; Mol wt: 247.2697

ACTION – Furan nitron compound for treating or preventing inflammatory bowel disease (IBD), shown to reduce TNBS-induced colonic inflammation by 25-44% at a dose of 10 mg/kg p.o. in rats. Other specifically claimed compounds include the following:



Compound	R1	Formula
283861	t-Bu	C ₉ H ₁₃ NO ₅ S
283862	C ₆ H ₁₃	C ₁₁ H ₁₇ NO ₅ S
283863	cyclohexyl	C ₁₁ H ₁₅ NO ₅ S
283864	1-adamantyl	C ₁₅ H ₁₉ NO ₅ S

Nitron-related therapeutics (NRTs) represent a novel approach to the treatment of IBD and other disorders characterized by an inappropriately strong and sustained immune response by their ability to mitigate oxidative stress by trapping free radicals.

SOURCE – Centaur.

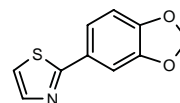
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1. Flitter, W.D. et al. (Centaur Pharmaceuticals, Inc.) *Furan nitron therapeutics for the treatment of inflammatory bowel disease*. WO 9959579.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

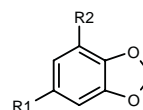
282683

2-(1,3-Benzodioxol-5-yl)thiazole



C₁₀H₇N O₂ S; Mol wt: 205.2363

ACTION – Hepatoprotectant reported to be effective in the CCl₄, D-galactosamine, thioacetamide and D-galactosamine/lipopolysaccharide models of hepatic injury in rodents following oral administration, as well as to be associated with low toxicity. Other exemplified dihydroxyphenyl derivatives include the following:



Compound	R1	R2	Formula
282686	CH=NOH	H	C ₈ H ₇ NO ₃
282687	2-Pyr-CH ₂ ON=CH	H	C ₁₄ H ₁₂ N ₂ O ₃
282689	2-Pyr-CH ₂ ON=CH	OMe	C ₁₅ H ₁₄ N ₂ O ₄
282690	COCH ₂ SAc	H	C ₁₁ H ₁₀ O ₄ S

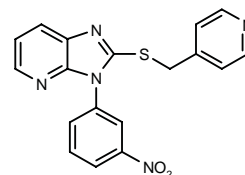
SOURCE – Choongwae.

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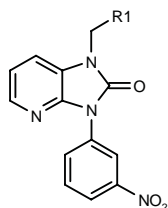
283676

3-(3-Nitrophenyl)-2-(4-pyridinylmethylsulfanyl)-3*H*-imidazo[4,5-*b*]pyridine

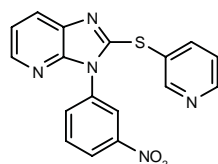


C₁₈H₁₃N₅O₂ S; Mol wt: 363.3997

ACTION – Hepatoprotective agent proven effective in murine models of concanavalin A (Con A)- and lipopolysaccharide/D-galactosamine-induced hepatic injury when administered orally at a dose of 30 mg/kg, as measured by attenuation of the increase in GPT (ALT) levels; it was also shown to be safe in rats, with no deaths in animals treated with doses of up to 2000 mg/kg p.o. Other representative compounds from this series of condensed imidazole derivatives are:



Compound	R1	Formula
283678	4-Pyr	C ₁₈ H ₁₃ N ₅ O ₃
283679	4-NH ₂ -Ph	C ₁₉ H ₁₅ N ₅ O ₃



283677: C₁₇ H₁₁ N₅ O₂ S

SOURCES – Nippon Chemiphar; Zeria.

REFERENCES

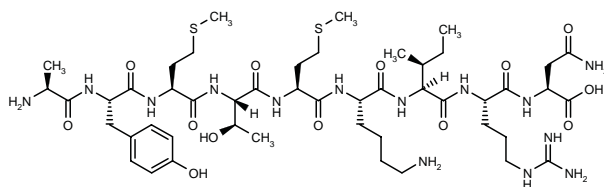
1. Nagasawa, M. et al. (Nippon Chemiphar Co., Ltd.; Zeria Pharmaceutical Co., Ltd.) Condensed imidazole deriv. and therapeutic agent for liver disease. WO 9957103.

TREATMENT OF PANCREATIC DISORDERS

IT-9302

283011

L-Alanyl-L-tyrosyl-L-methionyl-L-threonyl-L-methionyl-L-lysyl-L-isoleucyl-L-arginyl-L-asparagine



C₄₈ H₈₂ N₁₄ O₁₃ S₂; Mol wt: 1127.3930

ACTION – IL-10 agonist, a nonapeptide with complete homology to a sequence of human IL-10 located in the C-terminal portion of the cytokine and significant IL-10-like properties *in vivo*. In a pig model of pancreatitis induced by chenodeoxycholic acid, compound, given before or after induction of acute necrotizing pancreatitis, significantly reduced TNF- α levels without affecting either amylase or IL-8 levels. Moreover, it significantly decreased the number of CD2+ cells and increased the number of CD45RO+ memory cells, without affecting the number of CD4+ or CD8+ cells or the CD4/CD8 ratio.

SOURCE – Nycomed Amersham.

REFERENCES

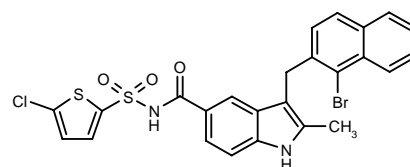
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2. Gronhoj Larsen, C. and Gesser, B. (Nycomed DAK A/S) Immunomodulators. WO 9601318.
3. Gesser, B. et al. Identification of functional domains on human interleukin-10. Proc Natl Acad Sci USA 1997, 94(26): 14620.
4. Lausten, S.B. et al. IT9302, a new IL-10 agonist, increases the number of circulating memory cells of CD45+ phenotype and decreases number of CD2+ cells and TNF- α in pigs with acute necrotizing pancreatitis. Gut 1999, 45(Suppl. 5): Abst P1243.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

282844

3-(1-Bromonaphthalen-2-ylmethyl)-N-(5-chlorothiophen-2-ylsulfonyl)-2-methyl-1H-indole-5-carboxamide



C₂₅ H₁₈ Br Cl N₂ O₃ S₂; Mol wt: 573.9172

ACTION – Hypoglycemic agent with inhibitory activity against phosphodiesterase type 5 (PDE5). It lowered blood glucose levels and triglycerides in *db/db* mice by 19 and 9%, respectively, at a dose of 3.2 mg/kg in the feed over 14 days.

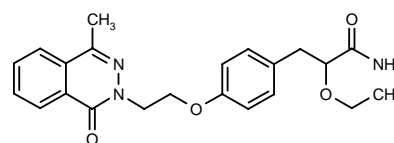
SOURCE – Fujisawa.

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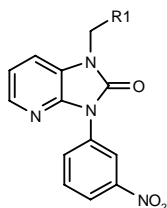
282979

2-Ethoxy-3-[4-[2-(4-methyl-1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propionamide

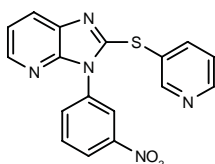


C₂₂ H₂₅ N₃ O₄; Mol wt: 395.4565

ACTION – Benzazepine derivative with potent hypoglycemic activity and insulin sensitivity-enhancing effects at least comparable to rosiglitazone (ED₂₅ = 3.7 and 4.6 mg/kg/day p.o., respectively, for hypoglycemic activity in *db/db* mice). Potentially useful for the treatment of type II diabetes.



Compound	R1	Formula
283678	4-Pyr	C ₁₈ H ₁₃ N ₅ O ₃
283679	4-NH ₂ -Ph	C ₁₉ H ₁₅ N ₅ O ₃



283677: C₁₇ H₁₁ N₅ O₂ S

SOURCES – Nippon Chemiphar; Zeria.

REFERENCES

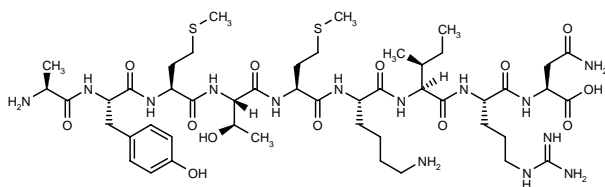
1. Nagasawa, M. et al. (Nippon Chemiphar Co., Ltd.; Zeria Pharmaceutical Co., Ltd.) *Condensed imidazole deriv. and therapeutic agent for liver disease*. WO 9957103.

TREATMENT OF PANCREATIC DISORDERS

IT-9302

283011

L-Alanyl-L-tyrosyl-L-methionyl-L-threonyl-L-methionyl-L-lysyl-L-isoleucyl-L-arginyl-L-asparagine



C₄₈ H₈₂ N₁₄ O₁₃ S₂; Mol wt: 1127.3930

ACTION – IL-10 agonist, a nonapeptide with complete homology to a sequence of human IL-10 located in the C-terminal portion of the cytokine and significant IL-10-like properties *in vivo*. In a pig model of pancreatitis induced by chenodeoxycholic acid, compound, given before or after induction of acute necrotizing pancreatitis, significantly reduced TNF- α levels without affecting either amylase or IL-8 levels. Moreover, it significantly decreased the number of CD2⁺ cells and increased the number of CD45RO⁺ memory cells, without affecting the number of CD4⁺ or CD8⁺ cells or the CD4/CD8 ratio.

SOURCE – Nycomed Amersham.

REFERENCES

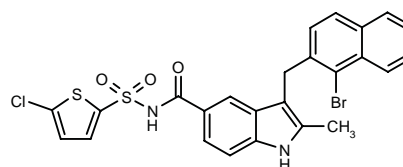
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2. Gronhoj Larsen, C. and Gesser, B. (Nycomed DAK A/S) *Immunomodulators*. WO 9601318.
3. Gesser, B. et al. *Identification of functional domains on human interleukin-10*. Proc Natl Acad Sci USA 1997, 94(26): 14620.
4. Lausten, S.B. et al. *IT9302, a new IL-10 agonist, increases the number of circulating memory cells of CD45⁺ phenotype and decreases number of CD2⁺ cells and TNF- α in pigs with acute necrotizing pancreatitis*. Gut 1999, 45(Suppl. 5): Abst P1243.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

282844

3-(1-Bromonaphthalen-2-ylmethyl)-N-(5-chlorothien-2-ylsulfonyl)-2-methyl-1H-indole-5-carboxamide



C₂₅ H₁₈ Br Cl N₂ O₃ S₂; Mol wt: 573.9172

ACTION – Hypoglycemic agent with inhibitory activity against phosphodiesterase type 5 (PDE5). It lowered blood glucose levels and triglycerides in *db/db* mice by 19 and 9%, respectively, at a dose of 3.2 mg/kg in the feed over 14 days.

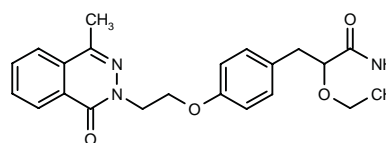
SOURCE – Fujisawa.

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282979

2-Ethoxy-3-[4-[2-(4-methyl-1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propionamide



C₂₂ H₂₅ N₃ O₄; Mol wt: 395.4565

ACTION – Benzazine derivative with potent hypoglycemic activity and insulin sensitivity-enhancing effects at least comparable to rosiglitazone (ED₂₅ = 3.7 and 4.6 mg/kg/day p.o., respectively, for hypoglycemic activity in *db/db* mice). Potentially useful for the treatment of type II diabetes.

SOURCE – SSP.

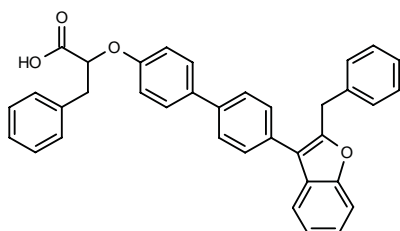
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283672

2-[4'-(2-Benzylbenzofuran-3-yl)biphenyl-4-yloxy]-3-phenylpropionic acid



C36 H28 O4; Mol wt: 524.6132

ACTION – Protein-tyrosine-phosphatase (PTPase) inhibitor (IC₅₀ = 0.27 μ M for inhibition of recombinant human PTP1B) shown to reduce blood glucose and insulin levels in diabetic mice by 40.4 and 44.9%, respectively, at a dose of 100 mg/kg/day by gavage. Potentially useful in the treatment of insulin resistance associated with diabetes mellitus, obesity, glucose intolerance, hypertension and vascular ischemic disorders, and hyperglycemia.

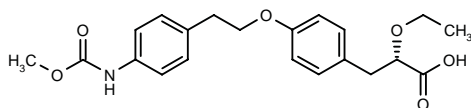
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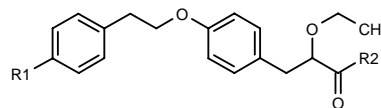
283956

2-(S)-Ethoxy-3-[4-[2-[4-(methoxycarboxamido)-phenyl]ethoxy]phenyl]propionic acid



C21 H25 N O6; Mol wt: 387.4295

ACTION – Insulin sensitizer shown to have increased potency and efficacy compared to troglitazone at the same oral dose as regards reductions in plasma glucose, insulin and triglycerides in obese diabetic *ob/ob* mice. Potentially useful for the treatment or prophylaxis of conditions associated with insulin resistance such as diabetes, dyslipidemia and obesity. Other specifically claimed 3-aryl-2-hydroxypropionic acid derivatives and analogues include the following:



Compound	R1	R2	Isomer	Formula
283957	t-BuNHCOO	OEt		C ₂₆ H ₃₅ NO ₆
283958	OSO ₂ Me	-NHCN		C ₂₁ H ₂₄ N ₂ O ₆ S
283959	OSO ₂ Me	NHOCH ₂ Ph		C ₂₇ H ₃₁ NO ₇ S
283960	t-BuCON(Me)	OH	S	C ₂₅ H ₃₃ NO ₅
283961	NHCO ₂ CH ₂ Ph	OH	S	C ₂₇ H ₂₉ NO ₆

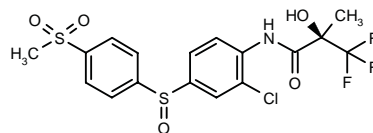
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REFERENCES

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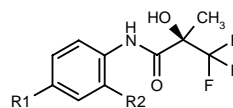
283967

N-[2-Chloro-4-[4-(methanesulfonyl)phenylsulfinyl]phenyl]-3,3,3-trifluoro-2-(R)-hydroxy-2-methylpropionamide



C17 H15 Cl F3 N O5 S2; Mol wt: 469.8865

ACTION – Compound with the ability to increase pyruvate dehydrogenase (PDH) activity and thus expected to be of value in the treatment of disease states associated with disorders of glucose utilization such as diabetes mellitus, obesity and lactic acidemia, as well as peripheral vascular disease, cardiac failure, cardiac myopathies, muscle weakness, hyperlipidemia, atherosclerosis and Alzheimer's disease. Other specifically claimed compounds are:



Compound	R1	R2	Formula
283969	4-(2-oxo-1-pyrrolidinyl)-PhSO ₂	Cl	C ₂₀ H ₁₈ ClF ₃ N ₂ O ₅ S
283972	4-(HOCH ₂ CH ₂ NH)-PhSO ₂	F	C ₁₈ H ₁₈ F ₄ N ₂ O ₅ S
283974	4-(HOCH ₂ CH ₂ NH)-PhSO ₂	Cl	C ₁₈ H ₁₈ ClF ₃ N ₂ O ₅ S
283975	4-(MeSCH ₂ CH ₂ NH)-PhSO ₂	Cl	C ₁₉ H ₂₀ ClF ₃ N ₂ O ₄ S ₂
283976	4-(MeSO)-PhSO	Cl	C ₁₇ H ₁₅ ClF ₃ N ₂ O ₄ S ₂
283977	SO ₂ CH ₂ CH ₂ OH	Cl	C ₁₂ H ₁₃ ClF ₃ N ₂ O ₅ S
283979	SO ₂ Et	Cl	C ₁₂ H ₁₃ ClF ₃ N ₂ O ₄ S
283980	4-[N(Me)2CO]-PhSO ₂	Cl	C ₁₉ H ₁₈ ClF ₃ N ₂ O ₅ S
283982	4-NH ₂ -PhSO ₂	Cl	C ₁₆ H ₁₄ ClF ₃ N ₂ O ₄ S

Pyruvate dehydrogenase is the key regulatory enzyme in controlling the rate of acetyl-CoA formation from glucose via its ability to catalyze the oxidation of pyruvate to acetyl-CoA and carbon dioxide, with concomitant reduction of nicotinamide adenine dinucleotide (NAD) to NADH.

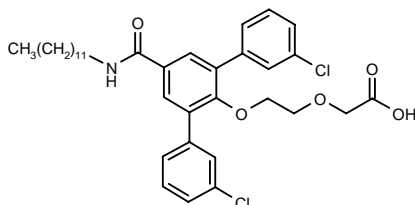
SOURCE – AstraZeneca.

REFERENCES

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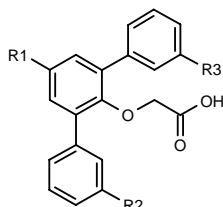
284062

2-[2-[2,6-Bis(3-chlorophenyl)-4-(dodecylcarbamoyl)phenoxy]ethoxy]acetic acid

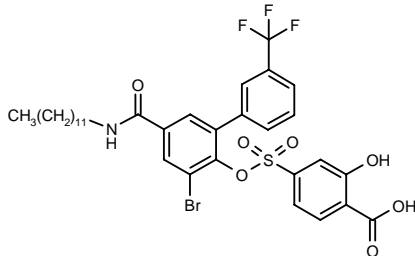


C35 H43 Cl2 N O5; Mol wt: 628.6327

ACTION – Protein-tyrosine-phosphatase (PTPase) inhibitor ($IC_{50} = 0.015 \mu M$ for inhibition of recombinant human PTP1B) expected to be of value in the treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic vascular disorders. Other representative compounds from this series of 2,3,5-substituted biphenyls include the following:



Compound	R1	R2	R3	Formula
284063	OC18H37	H	H	C ₃₈ H ₅₂ O ₄
284064	2-(C16H33NH)-3,4-dioxo-1-cyclobutenyl-NH	H	H	C ₄₀ H ₅₀ N ₂ O ₅
284066	2,4-(F)2-PhO(CH2)12NHCO	Cl	Cl	C ₃₉ H ₄₁ Cl ₂ F ₂ NO ₅
284067	C13H27	H	H	C ₃₃ H ₄₂ O ₃
284068	OC14H29	H	H	C ₃₄ H ₄₄ O ₄



284069: C33 H37 Br F3 N O7 S

SOURCE – American Home Products.

REFERENCES

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INSULIN ASPART

Prop INN

134086

28^B-L-Aspartic acid-insulin (human)

ACTION – Recombinant rapid-acting insulin analogue.

INDICATION – Treatment of diabetes mellitus.

PRESENTATION – Vials (10 ml) of solution for injection, 100 U/ml; Penfill® cartridges (1.5 and 3 ml) of solution for injection, 100 U/ml; NovoLet® prefilled syringes (1.5 and 3 ml) of solution for injection, 100 U/ml.

PROPRIETARY NAME – NovoRapid (GB).

SOURCE – Novo Nordisk.

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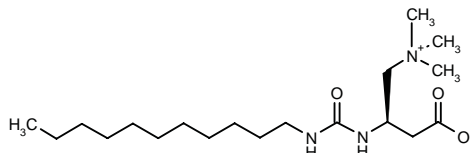
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ST-1327

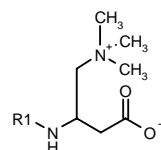
283416

4-(Trimethylammonium)-3(R)-(3-undecylureido)butyrate



C19 H39 N3 O3; Mol wt: 357.5351

ACTION – Agent for the treatment of hyperglycemia, diabetes and related disorders such as diabetic retinopathy and diabetic neuropathy, as well as cardiovascular disorders such as heart failure and ischemia, a reversible inhibitor of carnitine palmitoyltransferase (CPT), particularly CPT I. Compound displayed an IC_{50} value of 3.2 μ M for inhibition of rat liver mitochondrial CPT I using palmitoyl-CoA and L-carnitine as the substrates, compared to a value of 17.4 μ M for the reference compound SDZ-CPI-975. Compound markedly decreased blood β -hydroxybutyrate and glucose levels in normal fasted rats at 14.5 mg/kg i.p. and was shown to significantly decrease blood glucose and insulin levels in diabetic rats fed a high-fat diet at 45 mg/kg p.o. b.i.d. x 20 days. Other exemplified compounds include the following:



Compound	R1	Isomer	Formula
ST-1326 [283417]	CONHC14H29	R	C ₂₂ H ₄₅ N ₃ O ₃
ST-1251 [283418]	CONHC9H19		C ₁₇ H ₃₅ N ₃ O ₃
ST-1364 [283419]	SO2C10H21		C ₁₇ H ₃₆ N ₂ O ₄ S

SOURCE – Sigma-Tau.

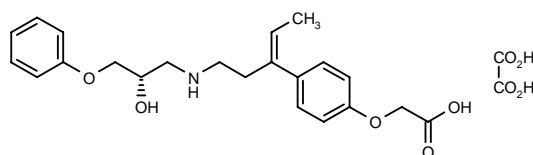
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SWR-0342SA

261624

2-[4-[1-[2-[2(S)-Hydroxy-3-phenoxypropylamino]ethyl]-1(Z)-propenyl]phenoxy]acetic acid oxalate



C22 H27 N O5 . C2 H2 O4; Mol wt: 475.4911

ACTION – Potent and selective β_3 -adrenoceptor (AR) agonist able to stimulate white adipocyte lipolysis (β_3 -AR activity; $EC_{50} = 1.2$ nM) and the atrial beating rate (β_1 -AR activity; $EC_{50} = 22.9$ nM), whereas it was inactive in relaxing rat uterine muscle (β_2 -AR activity; $EC_{50} > 10,000$ nM). Compound enhanced the accumulation of cAMP in CHO cells expressing human β_1 - and β_3 -AR with about 35 times higher efficacy in the latter ($EC_{50} = 196.1$ and 5.4 nM, respectively), while having no effect in CHO cells expressing human β_2 -AR ($EC_{50} > 10$ μ M). In KKA^y mice, an animal model of obesity and non-insulin-dependent diabetes mellitus, at a dose of 1 mg/kg/day p.o. for 14 days, it had no effect on body weight or food intake but produced a slight decrease in the weight of fat pads, and significantly reduced blood glucose (about 54%) and serum insulin levels (about 60%). Potentially useful for the treatment of diabetes.

SOURCE – Sawai.

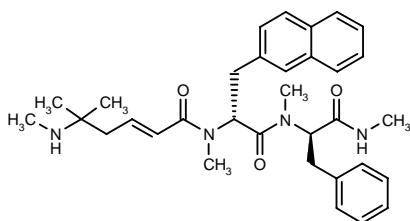
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TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

281401

N-[*N*-[5-Methyl-5-(methylamino)-2(*E*)-hexenoyl]-*N*-methyl-3-(2-naphthyl)-D-alanyl]-*N*-methyl-D-phenylalanine methylamide



C33 H42 N4 O3; Mol wt: 542.7198

ACTION – Growth hormone secretagogue, a peptidomimetic amino acid derived from ipamorelin with nanomolar activity *in vitro* ($EC_{50} = 3$ -10 nM in a rat pituitary assay).

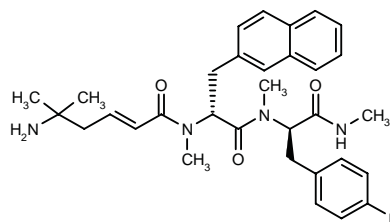
SOURCE – Novo Nordisk.

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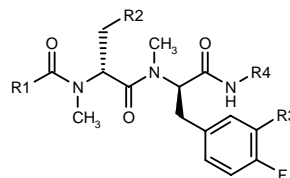
282296

N-[*N*-[5-Amino-5-methyl-2(*E*)-hexenoyl]-*N*-methyl-3-(2-naphthyl)-D-alanyl]-*N*-methyl-D-(4-fluoro)phenylalanine methylamide



C32 H39 F N4 O3; Mol wt: 546.6831

ACTION – Growth hormone secretagogue with improved resistance to proteolytic degradation as compared to previously disclosed peptides by virtue of its non-natural amide bond mimetics and thus expected to exhibit improved bioavailability. Other specifically claimed compounds from this series of peptide mimetics include the following:



Compound	R1	R2	R3	R4	Formula
282297	3-[NH2CH(Me)]-Ph	4-Ph-Ph	F	Me	C ₃₆ H ₃₈ F ₂ N ₄ O ₃
282298	(E)-1-NH2-1-cyclobutyl-CH2CH=CH	2-Naph	F	CH2CH2Ph	C ₄₀ H ₄₄ F ₂ N ₄ O ₃
282299	3-[NH2CH(Me)]-Ph	4-Ph-Ph	H	CH2C(Me)2-CH2OH	C ₄₀ H ₄₇ FN ₄ O ₄
282300	(E)-1-NH2-1-cyclobutyl-CH2CH=CH	2-Naph	H	(R)-CH2-CH(OH)Me	C ₃₆ H ₄₃ FN ₄ O ₄
282301	3-(NH2CH2)-Ph	2-Naph	H	CH2CH2Ph	C ₄₀ H ₄₁ FN ₄ O ₃
282302	(E)-CH=CHCH2-C(Me)2NHMe	2-Naph	F	CH2CH2Ph	C ₄₀ H ₄₆ F ₂ N ₄ O ₃
282303	(E)-CH=CHCH2-C(Me)2NHMe	2-Naph	H	(R)-CH2-CH(OH)Me	C ₃₆ H ₄₅ FN ₄ O ₄

SOURCE – Novo Nordisk.

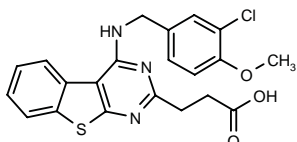
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TREATMENT OF MALE SEXUAL DYSFUNCTION

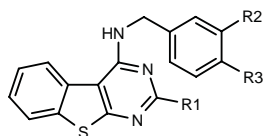
282650

3-[4-(3-Chloro-4-methoxybenzylamino)[1]benzothieno-[2,3-*d*]pyrimidin-2-yl]propionic acid



C₂₁ H₁₈ Cl N₃ O₃ S; Mol wt: 427.9102

ACTION – An inhibitor of cGMP-phosphodiesterase (PDE5) with potential in the treatment or prevention of cardiovascular disorders and erectile dysfunction. Other specifically claimed compounds from this series of condensed thienopyrimidines include the following:



Compound	R1	R2	R3	Formula
282651	(CH ₂) ₃ CO ₂ H	-OCH ₂ O-		C ₂₂ H ₁₉ N ₃ O ₄ S
282652	(CH ₂) ₆ CO ₂ H	-OCH ₂ O-		C ₂₅ H ₂₅ N ₃ O ₄ S
282653	(CH ₂) ₆ CO ₂ H	Cl	OMe	C ₂₅ H ₂₆ ClN ₃ O ₃ S
282654	(CH ₂) ₄ CO ₂ H	Cl	OMe	C ₂₃ H ₂₂ ClN ₃ O ₃ S
282655	4-(CO ₂ HCH ₂)-cyclohexyl	Cl	OMe	C ₂₆ H ₂₆ ClN ₃ O ₃ S
282656	4-CO ₂ H-cyclohexyl	-OCH ₂ O-		C ₂₅ H ₂₃ N ₃ O ₄ S
282657	4-CO ₂ H-Ph	-OCH ₂ O-		C ₂₅ H ₁₇ N ₃ O ₄ S
282658	4-(CO ₂ HCH ₂)-Ph	-OCH ₂ O-		C ₂₆ H ₁₉ N ₃ O ₄ S

SOURCE – Merck KGaA.

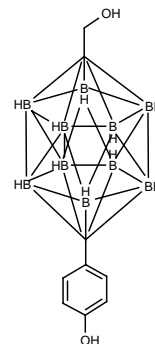
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TREATMENT OF GYNECOLOGICAL DISORDERS

283080

12-(4-Hydroxyphenyl)-1,12-dicarba-closo-dodecaborane(12)-1-methanol



C₉ H₁₈ B₁₀ O₂; Mol wt: 266.3492

ACTION – Estrogen agonist with a potency at least 10-fold greater than 17β-estradiol in a luciferase reporter gene assay using rat estrogen ERα receptors; compound showed high affinity for the ERα receptor (K_i = 0.1 nM), slightly superior to 17β-estradiol (K_i = 0.4 nM). Selected as a lead for further development of selective estrogen agonists with potential as therapeutic agents for a variety of female hormonal diseases.

SOURCE – University of Tokyo, Tokyo (JP).

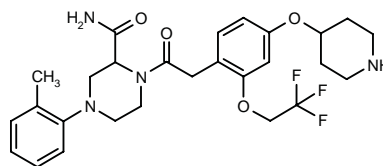
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UTERINE STIMULANTS AND TOCOLYTICS

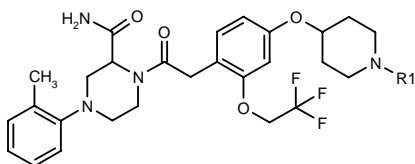
282259

4-(2-Methylphenyl)-1-[2-[4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenyl]acetyl]piperazine-2-carboxamide



C₂₇ H₃₃ F₃ N₄ O₄; Mol wt: 534.5757

ACTION – Oxytocin receptor antagonist with application in the treatment of preterm labor, for stopping labor prior to cesarean delivery and for the treatment of dysmenorrhea due to its ability to relax uterine contractions. Other specifically claimed piperazine compounds are:



Compound	R1	Formula
282260	cyclopropyl-CH ₂	C ₃₁ H ₃₉ F ₃ N ₄ O ₄
282261	SO ₂ Me	C ₂₈ H ₃₅ F ₃ N ₄ O ₆ S
282262	Ac	C ₂₉ H ₃₅ F ₃ N ₄ O ₅
282263	CH ₂ C(Me)2OH	C ₃₁ H ₄₁ F ₃ N ₄ O ₅

SOURCE – Merck & Co.

REFERENCES

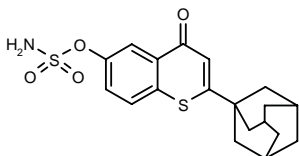
1. Williams, P.D. et al. (Merck & Co., Inc.) *Piperazine oxytocin receptor antagonists*. US 5968938.

DERMATOLOGIC DRUGS

ACNE THERAPY

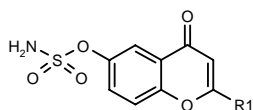
282155

Sulfamic acid 2-(1-adamantyl)-4-oxo-4*H*-1-benzothio-
pyran-6-yl ester



C₁₉ H₂₁ N O₄ S₂; Mol wt: 391.5099

ACTION – Steroid sulfatase inhibitor with potential in the treatment of androgen-dependent disorders such as acne, seborrhea, androgenic alopecia and hirsutism, and in the topical treatment of squamous cell carcinoma. *In vitro*, compound exhibited a relative IC₅₀ (IC₅₀ compound/IC₅₀ estrone sulfamate) of 0.0064 in an assay determining inhibition of steroid sulfatase purified from human placenta. Other specifically claimed compounds from this series of chromanone and thiochromanone derivatives include the following:



Compound	R1	Formula
282156	t-Bu	C ₁₃ H ₁₅ NO ₅ S
282157	1-adamantyl	C ₁₉ H ₂₁ NO ₅ S

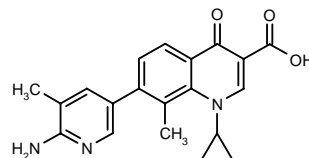
SOURCE – Novartis.

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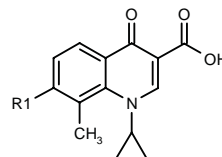
282845

7-(6-Amino-5-methylpyridin-3-yl)-1-cyclopropyl-8-methyl-
4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C₂₀ H₁₉ N₃ O₃; Mol wt: 349.3881

ACTION – Quinolone antibacterial with potent activity against Gram-positive bacteria, particularly *Propionibacterium acnes*, giving MIC values against *P. acnes* JCM6425 and *Staphylococcus aureus* F-1924 of 0.0078 and 0.1 µg/ml, respectively; it proved to be nontoxic in several assays. Other exemplified compounds are:

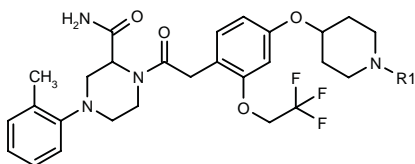


Compound	R1	Formula
282846	2,6-(Me)2-4-Pyr	C ₂₁ H ₂₀ N ₂ O ₃
282847	6-Me-3-Pyr	C ₂₀ H ₁₈ N ₂ O ₃
282848	5-Me-6-(MeNH)-3-Pyr	C ₂₁ H ₂₁ N ₃ O ₃

SOURCE – Toyama.

REFERENCES

1. Hayashi, K. et al. (Toyama Chemical Co., Ltd.) *Quinolonecarboxylic acid derivs. or salts thereof*. WO 9951588.



Compound	R1	Formula
282260	cyclopropyl-CH ₂	C ₃₁ H ₃₉ F ₃ N ₄ O ₄
282261	SO ₂ Me	C ₂₈ H ₃₅ F ₃ N ₄ O ₆ S
282262	Ac	C ₂₉ H ₃₅ F ₃ N ₄ O ₅
282263	CH ₂ C(Me)2OH	C ₃₁ H ₄₁ F ₃ N ₄ O ₅

SOURCE – Merck & Co.

REFERENCES

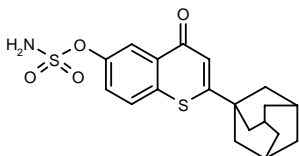
1. Williams, P.D. et al. (Merck & Co., Inc.) *Piperazine oxytocin receptor antagonists*. US 5968938.

DERMATOLOGIC DRUGS

ACNE THERAPY

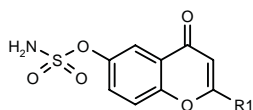
282155

Sulfamic acid 2-(1-adamantyl)-4-oxo-4*H*-1-benzothio-
pyran-6-yl ester



C₁₉H₂₁N O₄ S₂; Mol wt: 391.5099

ACTION – Steroid sulfatase inhibitor with potential in the treatment of androgen-dependent disorders such as acne, seborrhea, androgenic alopecia and hirsutism, and in the topical treatment of squamous cell carcinoma. *In vitro*, compound exhibited a relative IC₅₀ (IC₅₀ compound/IC₅₀ estrone sulfamate) of 0.0064 in an assay determining inhibition of steroid sulfatase purified from human placenta. Other specifically claimed compounds from this series of chromanone and thiochromanone derivatives include the following:



Compound	R1	Formula
282156	t-Bu	C ₁₃ H ₁₅ NO ₅ S
282157	1-adamantyl	C ₁₉ H ₂₁ NO ₅ S

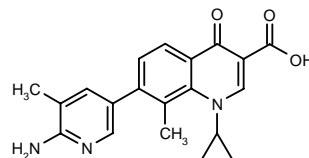
SOURCE – Novartis.

REFERENCES

1. Billich, A. et al. (Novartis AG) *Chromanone and thiochromanone derivs*. WO 9952890.

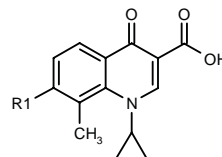
282845

7-(6-Amino-5-methylpyridin-3-yl)-1-cyclopropyl-8-methyl-
4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C₂₀H₁₉N₃O₃; Mol wt: 349.3881

ACTION – Quinolone antibacterial with potent activity against Gram-positive bacteria, particularly *Propionibacterium acnes*, giving MIC values against *P. acnes* JCM6425 and *Staphylococcus aureus* F-1924 of 0.0078 and 0.1 µg/ml, respectively; it proved to be nontoxic in several assays. Other exemplified compounds are:



Compound	R1	Formula
282846	2,6-(Me)2-4-Pyr	C ₂₁ H ₂₀ N ₂ O ₃
282847	6-Me-3-Pyr	C ₂₀ H ₁₈ N ₂ O ₃
282848	5-Me-6-(MeNH)-3-Pyr	C ₂₁ H ₂₁ N ₃ O ₃

SOURCE – Toyama.

REFERENCES

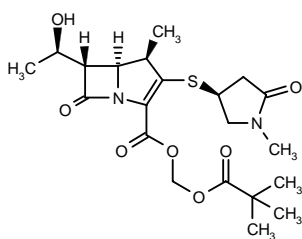
1. Hayashi, K. et al. (Toyama Chemical Co., Ltd.) *Quinolonecarboxylic acid derivs. or salts thereof*. WO 9951588.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

282022^{1,2,4}

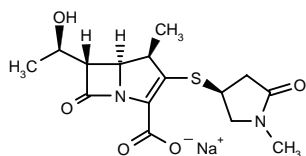
(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[1-methyl-5-oxopyrrolidin-3(*S*)-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid pivaloyloxymethyl ester



C21 H30 N2 O7 S; Mol wt: 454.5410

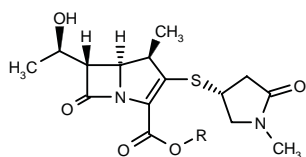
M.p. 137 °C; $[\alpha]_D^{23}$ -3.4° (*c* 1.0, MeOH).

ACTION – Orally active ester prodrug of a carbapenem [284695] that displayed a broad spectrum of activity against Gram-positive and Gram-negative bacteria (MIC < 0.01-0.8 µg/ml) and moderate activity against methicillin-resistant *Staphylococcus aureus* and cefdinir-resistant *Pseudomonas aeruginosa* (MIC = 12.5 and 25 µg/ml, respectively). The ester derivative showed favorable oral pharmacokinetics in mice after oral administration (50 mg/kg p.o.), with good oral absorption (absolute bioavailability = 55.34%) and prolonged half-lives. Compound showed good protection in mice infected with *S. aureus* Smith, *Escherichia coli* 704 and *Klebsiella pneumoniae* 866 (ED₅₀ = 1.21, 0.46 and 2.01 mg/kg, respectively), with higher potency than cefdinir (ED₅₀ = 5.94, 14.1 and 9.46 mg/kg, respectively).



284695^{1,3,4}: C15 H19 N2 Na O5 S

Another carbapenem and an orally active ester prodrug thereof are also described:



Compound	R	Formula
284696 ^{1,3,4}	Na	C ₁₅ H ₁₉ N ₂ NaO ₅ S
282021 ^{1,2,4}	t-BuCOOCH ₂	C ₂₁ H ₃₀ N ₂ O ₇ S

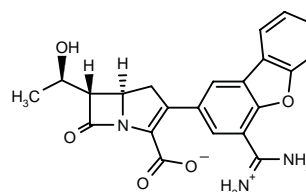
SOURCE – Sankyo.

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- Kanno, O. et al. Synthesis and biological evaluation of new oral carbapenems with 1-methyl-5-oxopyrrolidin-3-ylthio moiety. J Antibiot 1999, 52(10): 900.

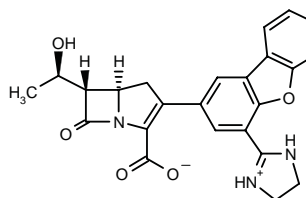
282059

(5*R*,6*S*)-2-(4-Amidinodibenzofuran-2-yl)-6-[1(*R*)-hydroxyethyl]-1-carba-2-penem-3-carboxylic acid inner salt



C22 H19 N3 O5; Mol wt: 405.4081

ACTION – Carbapenem antibiotic with excellent activity against methicillin-resistant *Staphylococcus aureus* (MRSA; MIC₉₀ = 2 µg/ml) and methicillin-resistant coagulase-negative staphylococci (MRCNS; MIC₉₀ = 2 µg/ml), and comparable or superior activity to vancomycin (MIC₉₀ = 2 and 8 µg/ml, respectively). In a murine systemic infection model, it demonstrated good efficacy against methicillin-susceptible *S. aureus* MB2985 (ED₅₀ < 0.096 mg/kg s.c.). Another related amidinium-substituted 2-dibenzofuranylcabapenem is:



231218: C24 H21 N3 O5

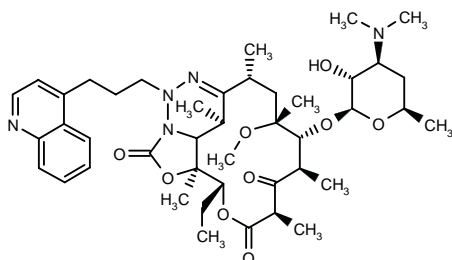
SOURCE – Merck & Co.

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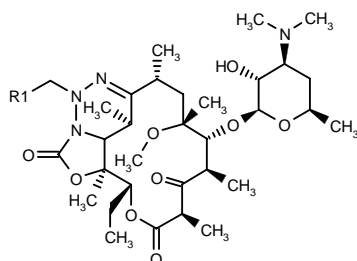
282122

9-Deoxy-11-deoxy-3-(descladinosyloxy)-9-imino-6-*O*-methyl-3-oxo-11-[2-[3-(quinolin-4-yl)propyl]hydrazino]-9a-*N*,11b-*N*-cycloerythromycin A 11a-*N*,12-*O*-cyclic carbamate



C43 H63 N5 O9; Mol wt: 793.9967

ACTION – Antibacterial and antiprotozoal agent from a series of 9a,11b-dehydro derivatives of 9-oxime-3-keto-6-*O*-methyl erythromycin A, wherein the following are also included:



Compound	R1	Formula
282123	Ph	C ₃₈ H ₅₈ N ₄ O ₉
282124	4-(3-Pyr)-1-imidazolyl-CH ₂ CH ₂	C ₄₂ H ₆₃ N ₇ O ₉

SOURCE – Pfizer.

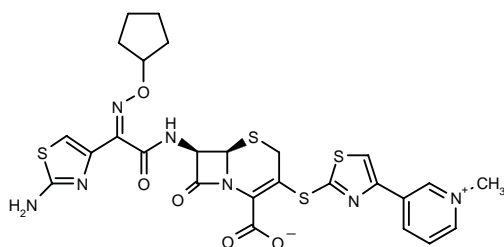
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1. Wu, Y.-J. (Pfizer Products Inc.) 9a,11b-Dehydro derivs. of 9-oxime-3-keto-6-*O*-methylerythromycin. EP 952157, JP 1999322777.

AM-1900^{2,3}

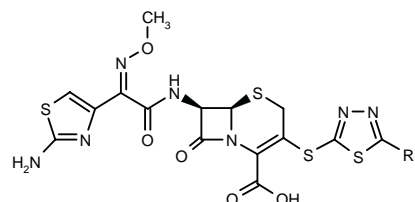
282992

(6*R*,7*R*)-7-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(cyclopentyl-oxyimino)acetamido]-3-[4-(1-methyl-3-pyridiniumyl)thiazol-2-ylsulfanyl]-3-cephem-4-carboxylate inner salt



C26 H25 N7 O5 S4; Mol wt: 643.7915

ACTION – Cephalosporin antibiotic designed based on molecular modeling of the penicillin-binding protein PBP2' structure and the cephalosporin CP-0467, with good activity against methicillin-resistant *Staphylococcus aureus* (MRSA; MIC = 0.78-3.13 µg/ml), as well as *Enterococcus faecalis* IID 682 and *Streptococcus pneumoniae* type III (MIC = 3.13 and 0.0063 µg/ml or less, respectively); compound was more active than CP-0467 against MRSA, *S. pneumoniae* and *E. faecalis* (MIC = 1.56-6.25, 0.0125 and 25 µg/ml, respectively). Other representative compounds within this series of cephalosporin antibiotics include the following:



Compound	R1	Formula
282994 ^{1,3}	Ph	C ₂₁ H ₁₇ N ₇ O ₅ S ₄
282995 ^{1,3}	2-thienyl	C ₁₉ H ₁₅ N ₇ O ₅ S ₅

SOURCE – Kyorin.

REFERENCES

1. Shiga, F. et al. (Kyorin Pharmaceutical Co., Ltd.) Anti-MRSA cephalosporin cpds. JP 1997278778.

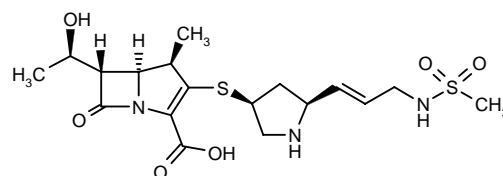
2. Shiga, F. et al. (Kyorin Pharmaceutical Co., Ltd.) Cephalosporin effective to MRSA. JP 1997278779.

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DA-1131

235904

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-[5(*S*)-[3-(methanesulfonamido)-1(*E*)-propenyl]pyrrolidin-3(*S*)-ylsulfanyl]-1-methyl-1-carba-2-penem-3-carboxylic acid



C18 H27 N3 O6 S2; Mol wt: 445.5583

ACTION – Carbapenem antibiotic with a broad spectrum of activity against both Gram-positive and Gram-negative bacteria and resistance to degradation by β-lactamases, and also relatively stable to hydrolysis by renal dehydropeptidase I (DHP-I) compared to imipenem and meropenem.

SOURCE – Dong-A.

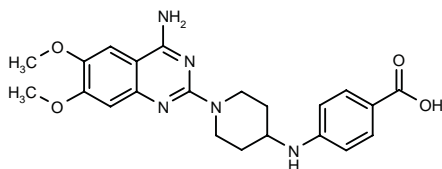
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ANTIBACTERIAL AGENTS

282198

4-[1-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperidin-4-ylamino]benzoic acid



C22 H25 N5 O4; Mol wt: 423.4705

ACTION – Antibacterial agent active against *Klebsiella pneumoniae* and *Staphylococcus aureus* (MIC = 6-12 µM), as well as against the mutant *Escherichia coli* imp-strain (MIC = 0.4-2 µM). Its *in vivo* antibacterial activity was moderate compared to gentamicin against *K. pneumoniae* infections in mice (40 and 70% survival rate at 100 and 3 mg/kg for compound and gentamicin, respectively). Compound appeared to act by altering RNA translation, as suggested by its ability to specifically inhibit luciferase-based bacterial transcription/translation (IC₅₀ = 12-12.5 µM) and to inhibit [³H]-UTP incorporation into RNA without altering RNA synthesis.

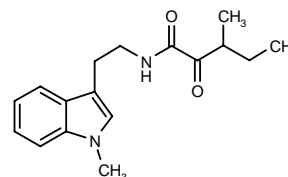
SOURCE – Isis Pharmaceuticals.

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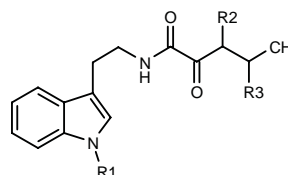
282324

3-Methyl-N-[2-(1-methyl-1H-indol-3-yl)ethyl]-2-oxopen-tanamide



C17 H22 N2 O2; Mol wt: 286.3728

ACTION – Antibacterial agent, an analogue of nematophin with excellent activity against Gram-positive bacteria, particularly staphylococci, giving MIC values of 0.015-2 µg/ml against clinical isolates of *Staphylococcus* spp., being more potent than nematophin (MIC = 0.25-8 µg/ml). Other compounds from this series of nematophin derivatives include the following:



Compound	R1	R2	R3	Formula
282325	Me	H	Me	C ₁₇ H ₂₂ N ₂ O ₂
282326	i-Pr	Me	H	C ₁₉ H ₂₆ N ₂ O ₂
282328	i-Pr	H	Me	C ₁₉ H ₂₆ N ₂ O ₂
282329	Ph	H	Me	C ₂₂ H ₂₄ N ₂ O ₂
282330	CH ₂ Ph	Me	H	C ₂₃ H ₂₆ N ₂ O ₂

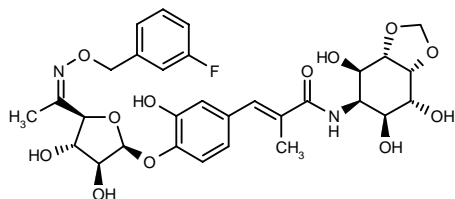
SOURCE – Bayer.

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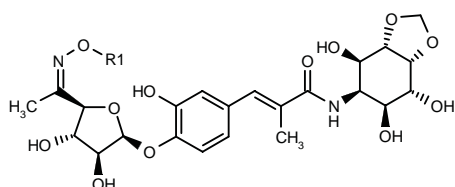
283019

3-[4-[5(*R*)-[1(*Z*)-(3-Fluorobenzyloxyimino)ethyl]-3(*S*),4(*S*)-dihydroxytetrahydrofuran-2(*S*)-yloxy]-3-hydroxyphenyl]-*N*-[(3*aS*,4*R*,5*R*,6*S*,7*R*,7*aR*)-4,6,7-trihydroxyperhydro-1,3-benzodioxol-5-yl]-2-methyl-2(*E*)-propenamide



C30 H35 F N2 O12; Mol wt: 634.6065

ACTION – Antibacterial and antiprotozoal hygromycin A derivative with activity against both Gram-negative and Gram-positive bacteria and protozoa. Other specifically claimed compounds include the following:



Compound	R1	Isomer	Formula
283020	cyclohexyl-CH2	E	C ₃₀ H ₄₂ N ₂ O ₁₂
283021	4-(NH ₂ CH ₂)-PhCH ₂	E	C ₃₁ H ₃₉ N ₃ O ₁₂
283022	3,4-dihydro-2H-1-benzopyran-4-yl-CH ₂	E	C ₃₃ H ₄₀ N ₂ O ₁₃
283023	4-MeO-PhCH ₂	E	C ₃₁ H ₃₈ N ₂ O ₁₃
283024	3-Cl-5-F-PhCH ₂	Z	C ₃₀ H ₃₄ ClF ₂ N ₂ O ₁₂
283025	6-Cl-1,3-benzodioxol-5-yl-CH ₂	Z	C ₃₁ H ₃₆ ClN ₂ O ₁₄
283026	7-F-1,2,3,4-tetrahydro-1-Naph	E	C ₃₃ H ₃₉ FN ₂ O ₁₂
283027	3-Cl-4-F-Ph	Z	C ₂₉ H ₃₂ ClFN ₂ O ₁₂
283028	5-Cl-2-thienyl-CH ₂	Z	C ₂₈ H ₃₃ ClN ₂ O ₁₂ S

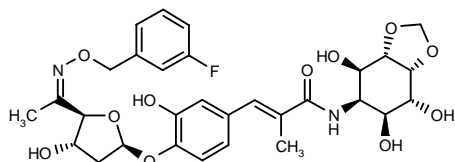
SOURCE – Pfizer.

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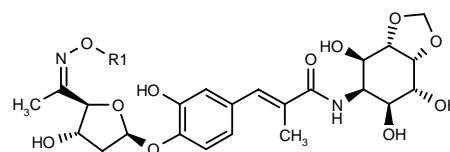
283031

3-[4-[5(*R*)-[1(*Z*)-(3-Fluorobenzyloxyimino)ethyl]-4(*S*)-hydroxytetrahydrofuran-2(*S*)-yloxy]-3-hydroxyphenyl]-*N*-[(3*aS*,4*R*,5*R*,6*S*,7*R*,7*aR*)-4,6,7-trihydroxyperhydro-1,3-benzodioxol-5-yl]-2-methyl-2(*E*)-propenamide



C30 H35 F N2 O11; Mol wt: 618.6075

ACTION – Antibacterial and antiprotozoal hygromycin A derivative with activity against both Gram-negative and Gram-positive bacteria and protozoa. Other specifically claimed compounds include the following:



Compound	R1	Isomer	Formula
283032	cyclohexyl-CH2	E	C ₃₀ H ₄₂ N ₂ O ₁₁
283033	5-benzofuryl-CH2	Z	C ₃₂ H ₃₆ N ₂ O ₁₂
283035	3-Cl-4-F-PhCH ₂	E	C ₃₀ H ₃₄ ClFN ₂ O ₁₁
283036	7-Cl-1,2,3,4-tetrahydro-1-Naph	Z	C ₃₃ H ₃₉ ClN ₂ O ₁₁
283037	2,4-(F)2-PhCH(Et)	E	C ₃₂ H ₃₈ F ₂ N ₂ O ₁₁
283039	3-Cl-4-F-Ph	E	C ₂₉ H ₃₂ ClFN ₂ O ₁₁
283040	2,3-(F)2-6-MeO-PhCH ₂	E	C ₃₁ H ₃₆ F ₂ N ₂ O ₁₂

SOURCE – Pfizer.

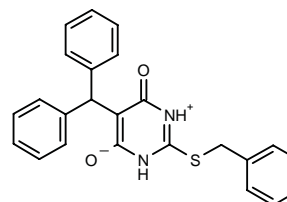
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INF-392

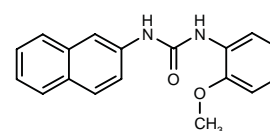
281967

5-(Diphenylmethyl)-6-oxo-2-(benzylsulfanyl)-3,6-dihydropyrimidin-1-ium-4-olate

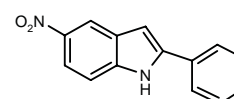


C24 H20 N2 O2 S; Mol wt: 400.5000

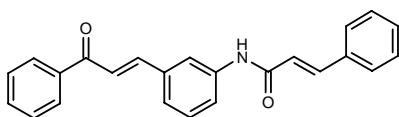
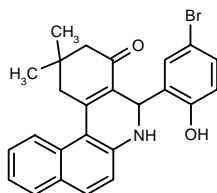
ACTION – An inhibitor of the NorA multidrug transporter that is able to reverse NorA-mediated resistance of a *Bacillus subtilis* strain to ethidium bromide and ciprofloxacin by 8-fold at a concentration of 0.4 µg/ml (32-fold lower than its MIC against this strain), and to reverse the resistance of *Staphylococcus aureus* SA1199B to ciprofloxacin by 4-fold at a concentration of 0.2 µg/ml (64-fold lower than its MIC against SA1199B). Compound was also shown to markedly reduce (50-fold or more) the frequency of spontaneous emergence of ciprofloxacin resistance in *S. aureus* SA1199. Potentially useful for enhancing the antibacterial activity of fluoroquinolones against resistant bacteria. Other NorA multidrug transporter inhibitors are:



INF-271 [281962]: C18 H16 N2 O2



INF-55 [281964]: C14 H10 N2 O2

INF-240 [281965]: C₂₄ H₁₉ N O₂INF-277 [281966]: C₂₅ H₂₂ Br N O₂

SOURCES – University of Chicago, Chicago, IL (US); Influx.

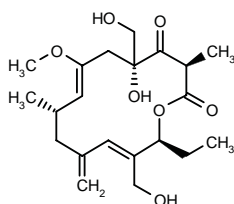
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ANTIFUNGAL AGENTS

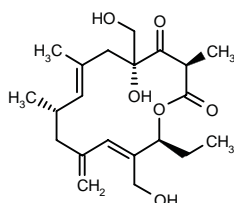
282116

14(*S*)-Ethyl-5(*S*)-hydroxy-5,13-bis(hydroxymethyl)-7-methoxy-3(*R*),9(*S*)-dimethyl-11-methyleneoxacyclo-tetradeca-7,12-diene-2,4-dione



C₂₁ H₃₂ O₇; Mol wt: 396.4768

ACTION – Antifungal agent, an analogue of galbonolide A with improved chemical stability, obtained by fermentation of *Streptomyces halstedii* MA7165 (ATCC 55946) in the presence of galbonolide A. Compound exhibited strong antifungal activity *in vitro* against *Cryptococcus neoformans* strains 2061 and 2062 (MIC₂₄ = 0.125 µg/ml; MIC₄₈ = 0.25 µg/ml), while showing much weaker activity against *Candida albicans* (MIC₂₄ = 32 µg/ml; MIC₄₈ > 32 µg/ml). Also disclosed is a galbonolide B analogue:



282117: C₂₁ H₃₂ O₆

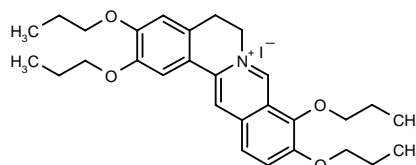
SOURCE – Merck & Co.

REFERENCES

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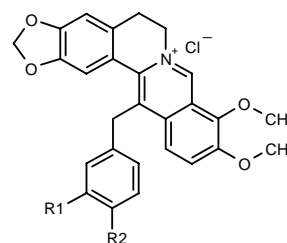
282643

2,3,9,10-Tetrapropoxy-5,6-dihydrodibenzo[*a,g*]quinolizinium iodide



C₂₉ H₃₈ I N O₄; Mol wt: 591.5222

ACTION – Topical antifungal agent, a protoberberine derivative with growth-inhibitory or fungicidal activity against cutaneous fungi such as *Epidermophyton*, *Microsporum*, *Trichophyton*, *Sporothrix schenckii*, *Aspergillus* and *Candida*. *In vitro*, compound exhibited MIC values of 0.4, 12.5 and 1.56 µg/ml against *Candida albicans* ATCC 11651, *Candida parapsilosis* and *Candida krusei*, respectively, as compared to respective MIC values of 3.125, 3.125 and 3.125 µg/ml for miconazole and 1.56, 3.125 and 0.78 µg/ml for amphotericin B. Compound was also shown to be effective against skin infections due to *Epidermophyton floccosum* in mice when applied as a 0.5% cream (70.5% efficacy at day 7 vs. 75.7% for 1% terbinafine cream). LD₅₀ > 5000 mg/kg p.o. in rats; no genotoxicity was observed in the Ames test. Other compounds from this series of protoberberine derivatives include the following:



Compound	R1	R2	Formula
282644	CF ₃	H	C ₂₈ H ₂₃ ClF ₃ NO ₄
282645	H	t-Bu	C ₃₁ H ₃₂ ClNO ₄
282646	H	i-Pr	C ₃₀ H ₃₀ ClNO ₄

SOURCE – Hanwha.

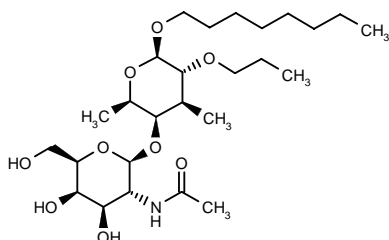
REFERENCES

1. Kim, J.H. et al. (Hanwha Corp.) Pharmaceutically available protoberberine salts derivs., and photoberberine derivs. and salts thereof. JP 1999302282, WO 9955704.

FIMBRIGAL P

282133

Octyl *O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→4)-2-*O*-propyl-β-D-galactopyranoside



C26 H49 N O9; Mol wt: 519.6711

ACTION – Antimicrobial agent, a derivative of βGalNAc(1→4)βGal that is especially active against *Candida* infections. It inhibits the binding of microbial fimbriae to epithelial cell targets to a significantly greater extent than the parent compound and demonstrated superior activity in a model of rat oral candidiasis.

SOURCE – Helix BioPharma.

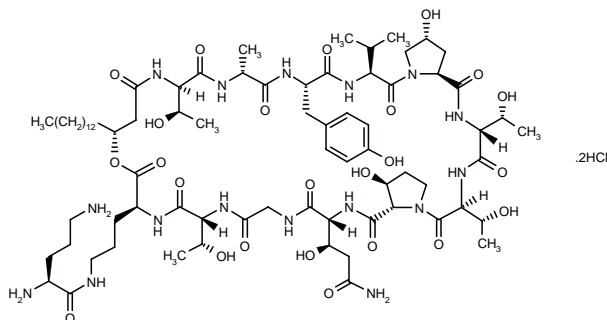
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FR-204042

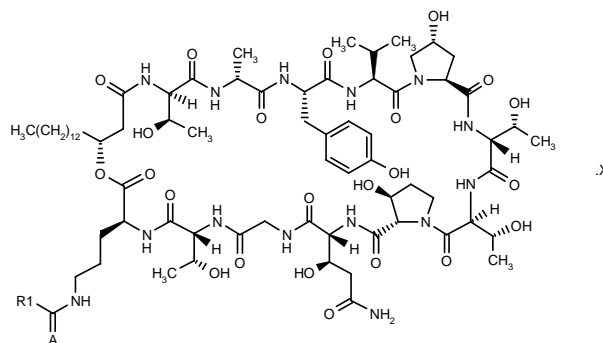
282963

[3*S*(1'*R*),6*R*(1'*R*),9*S*,11*R*,15*S*,18*S*,21*R*,24*R*(1'*R*),28*R*,31*S*,34*R*(1'*R*),40*R*(1'*R*),44*S*)-31-[3-[2(*S*),5-Diaminopentanamido]propyl]-40-(2-carbamoyl-1-hydroxyethyl)-11,44-dihydroxy-18-(4-hydroxybenzyl)-3,6,24,34-tetrakis(1-hydroxyethyl)-15-isopropyl-21-methyl-28-tridecyl-29-oxa-1,4,7,13,16,19,22,25,32,35,38,41-dodecaazatricyclo[41.3.0.0^{9,13}]hexatetracotane-2,5,8,14,17,20,23,26,30,33,36,39,42-tridecaone dihydrochloride



C76 H126 N16 O24 . 2HCl; Mol wt: 1720.8410

ACTION – Antifungal agent, a 1,3-β-glucan synthase inhibitor proven to dose-dependently protect mice from lethal infection with *Candida albicans* FP633. Other FR-901469 derivatives include the following:



Compound	R1	A	X	Formula
FR-200884 [282964]	3-azetidiny	O	HCl	C ₇₅ H ₁₂₁ N ₁₅ O ₂₄ .HCl
FR-205236 [282965]	3-azetidiny	NH	2HCl	C ₇₅ H ₁₂₂ N ₁₆ O ₂₃ .2HCl
FR-204021 [282966]	1,2-(Me)2-4-pyrazoly-CH2	NH	Cl ⁺ .HCl	C ₇₈ H ₁₂₆ N ₁₇ O ₂₃ .HCl

SOURCE – Fujisawa.

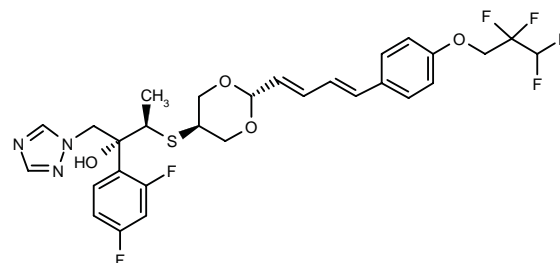
REFERENCES

1. Barrett, D. et al. *Synthesis and biological activity of novel 1,3-β-glucan synthase inhibitors derived from FR901469, an antifungal antibiotic.* 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 2P-14.

R-102557*

244175

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[*trans*-2-[4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]buta-1(*E*),3(*E*)-dienyl]-1,3-dioxan-5-ylsulfany]-1-(1,2,4-triazol-1-yl)-2-butanol



C29 H29 F6 N3 O4 S; Mol wt: 629.6270

ACTION – Orally active antifungal agent with excellent activity *in vivo* in murine models of systemic infections caused by *Candida albicans*, *Aspergillus fumigatus*, *Aspergillus flavus* and *Cryptococcus neoformans*, exhibiting activity superior to itraconazole when given at doses of 20-25 mg/kg p.o.

SOURCE – Sankyo.

REFERENCES

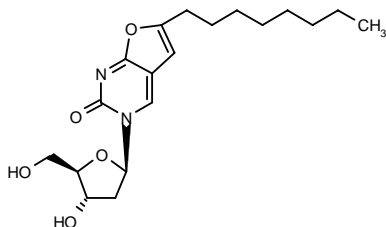
1. Oida, S. et al. (Sankyo Co., Ltd.) *Medicines containing triazole derivs.* JP 1998158167.
 2. Oida, S. et al. (Sankyo Co., Ltd.) *Triazole antifungal agent.* EP 841327, JP 1996333350, US 5977152, WO 9631491.
 3. Oida, S. et al. *Synthesis and antifungal activity of R-102557, a novel dioxane-triazole compound.* 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 2P-15.

*Identified compound **244175** (see **243696**) Drug Data Rep 1997, 019(02): 0151.

ANTIVIRAL DRUGS

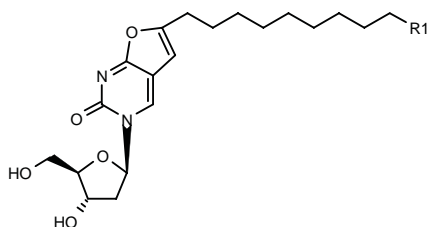
282173

3-(2'-Deoxy-β-D-ribofuranosyl)-6-octyl-2,3-dihydrofuro[2,3-d]pyrimidin-2-one



C₁₉ H₂₈ N₂ O₅; Mol wt: 364.4392

ACTION – Antiviral agent, a potent and selective inhibitor of varicella-zoster virus (VZV; EC₅₀ = 0.008 and 0.024 μM against OKA and YS strains, respectively), being approximately 300-fold more potent than aciclovir; it was completely inactive against herpes simplex virus type 1 and 2 (HSV-1, HSV-2), cytomegalovirus and vaccinia virus and showed no cytotoxicity up to 200 μM. Within this series of deoxynucleoside analogues, the following are also included:



Compound	R1	Formula
282175	H	C ₂₀ H ₃₀ N ₂ O ₅
282176	Me	C ₂₁ H ₃₂ N ₂ O ₅

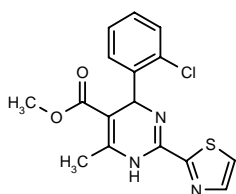
SOURCES – Cardiff University, Cardiff (GB); Rega Institute for Medical Research, Leuven (BE).

REFERENCES

- McGuigan, C. et al. (University College, Cardiff) *Anti-viral pyrimidine nucleoside analogues*. WO 9849177.
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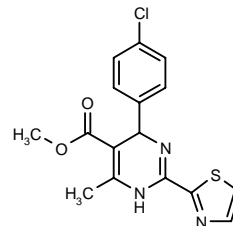
282304

4-(2-Chlorophenyl)-6-methyl-2-(2-thiazolyl)-1,4-dihydropyrimidine-5-carboxylic acid methyl ester



C₁₆ H₁₄ Cl N₃ O₂ S; Mol wt: 347.8246

ACTION – Antiviral agent particularly for the treatment of acute or chronic hepatitis B virus infections. Another compound from this series of 2-heterocyclically substituted dihydropyrimidines is:



282305: C₁₆ H₁₄ Cl N₃ O₂ S

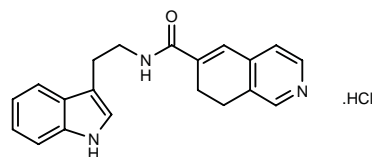
SOURCE – Bayer.

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- Goldmann, S. et al. (Bayer AG) *Novel 2-heterocyclically subst. dihydropyrimidines*. DE 19817262, WO 9954329.

282526

N-[2-(1*H*-Indol-3-yl)ethyl]-7,8-dihydroisoquinoline-6-carboxamide hydrochloride



C₂₀ H₁₉ N₃ O . HCl; Mol wt: 353.8510

ACTION – Antiviral agent active against human cytomegalovirus (HCMV; IC₅₀ = 0.1 μg/ml), with a good pharmacokinetic profile in mice. Compound showed good absorption after i.p. (100%), s.c. (62%) and p.o. (69%) administration and a relatively long elimination half-life of 57 min following an oral dose of 50 mg/kg. As demonstrated in rat, monkey and human liver preparations, the compound was stable to first-pass metabolism, unlike related compounds. A promising lead for further molecular design and optimization.

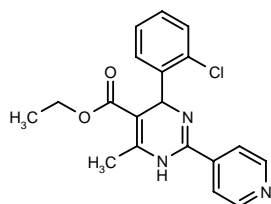
SOURCE – BioChem Pharma.

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- Chen, Y. et al. *Pharmacokinetics of a potent and selective HCMV inhibitor: 7,8-Dihydro-isoquinoline-6-carboxylic acid [2-(1*H*-indol-3-yl)-ethyl]-amide HCl (compound D)*. Annu Meet Am Assoc Pharm Sci (Nov 14-18, New Orleans) 1999, Abst 1116.

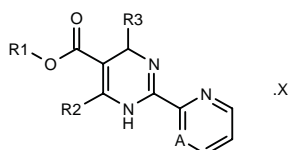
282728

4-(2-Chlorophenyl)-6-methyl-2-(4-pyridyl)-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester



C₁₉ H₁₈ Cl N₃ O₂; Mol wt: 355.8232

ACTION – Antiviral agent for the treatment of hepatitis B virus (HBV) infections, a representative compound from a series of dihydropyrimidines, wherein the following are also specifically claimed:



Compound	R1	R2	R3	A	X	Formula
282730	Me	Me	2-MeO-Ph	CH		C ₁₉ H ₁₉ N ₃ O ₃
282733	Me	CH ₂ CH ₂ CONHPh	2-Cl-Ph	CH		C ₂₆ H ₂₃ ClN ₄ O ₃
282735	Me	Me	4-F-2-NO ₂ -Ph	CH		C ₁₈ H ₁₅ FN ₄ O ₄
282737	Me	Me	2,4-(Cl) ₂ -Ph	N		C ₁₇ H ₁₄ Cl ₂ N ₄ O ₂
282739	Me	Me	2-Cl-3-thienyl	CH		C ₁₆ H ₁₄ ClN ₃ O ₂ S
282740	t-Bu	Me	2-Cl-Ph	CH		C ₂₁ H ₂₂ ClN ₃ O ₂
282741	Et	SCH ₂ CH ₂ OH	2-Cl-Ph	CH		C ₂₀ H ₂₀ ClN ₃ O ₃ S
282744	Et	Me	2-(2-Cl-PhS)-Ph	CH	HCl	C ₂₈ H ₂₂ ClN ₃ O ₂ S .HCl

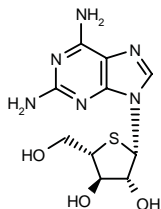
SOURCE – Bayer.

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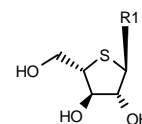
283414

9-(4-Thia-β-L-arabinofuranosyl)purine-2,6-diamine



C₁₀ H₁₄ N₆ O₃ S; Mol wt: 298.3256

ACTION – Agent for the treatment of hepatitis B virus (HBV) infections with an EC₅₀ value of 4.3 μg/ml in HBV-transfected human hepatocarcinoma HB611 cells and low cytotoxicity (CC₅₀ > 100 μg/ml). Other compounds from this series of L-4'-arabinofuranonucleoside derivatives include the following:



Compound	R1	Formula
283415	cytosin-1-yl	C ₉ H ₁₃ N ₃ O ₄ S
283421	thymine-1-yl	C ₁₀ H ₁₄ N ₂ O ₅ S
283423	2,6-(NH ₂) ₂ -purin-9-yl	C ₁₀ H ₁₄ N ₆ O ₃ S
283426	adenine-9-yl	C ₁₀ H ₁₃ N ₅ O ₃ S

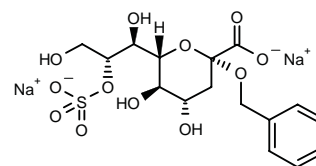
SOURCE – Rational Drug Design Laboratories, Fukushima (JP).

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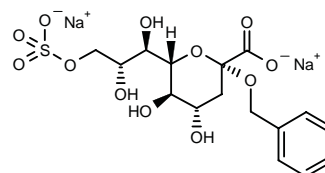
283997

2-O-Benzyl-3-deoxy-8-O-sulfo-α-D-glycero-D-galacto-2-nonulopyranosonic acid disodium salt



C₁₆ H₂₀ Na₂ O₁₂ S; Mol wt: 482.3680

ACTION – Antiviral agent with excellent activity against influenza A virus infection in MDCK cells and little or no cytotoxicity in uninfected cells. It increased survival in a murine model of influenza A virus infection when given intranasally. Another representative compound from this series of KDN (2-keto-3-deoxy-D-glycero-D-galactononulonic acid) derivatives is:



283998: C₁₆ H₂₀ Na₂ O₁₂ S

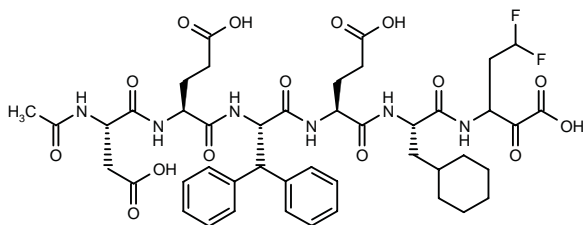
SOURCES – Kitasato Institute, Tokyo (JP); Meiji Milk Products.

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1. Furuhashi, K. et al. (Meiji Milk Products Co., Ltd.; Kitasato Institute) *Novel KDN derivs. and drugs containing the same as the active ingredient*. WO 9943689.

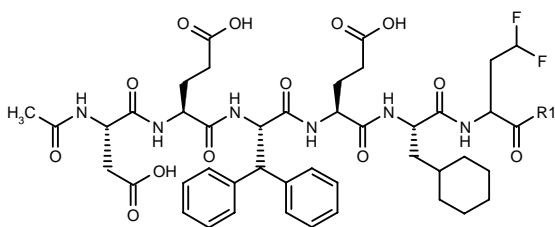
284448

3-[*N*-Acetyl-L-aspartyl-L-glutamyl-L-(3,3-diphenyl)alanyl-L-glutamyl-L-(3-cyclohexyl)alanyl]-5,5-difluoro-2-oxopentanoic acid



C45 H56 F2 N6 O15; Mol wt: 958.9604

ACTION – Agent for the treatment of disorders caused by hepatitis C virus (HCV) that acts by inhibiting HCV NS3 protease ($IC_{50} = 0.4$ nM). Other compounds from this series of fluorinated oligopeptides include the following:



Compound	R1	Formula
284449	OH	C ₄₄ H ₅₆ F ₂ N ₆ O ₁₄
284450	H	C ₄₄ H ₅₆ F ₂ N ₆ O ₁₃

SOURCE – Istituto di Ricerche di Biologia Molecolare P. Angeletti, Pomezia (IT).

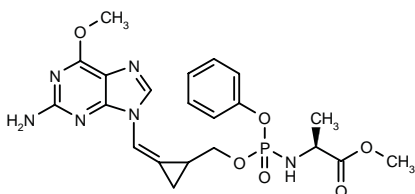
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QYL-972³**281960**

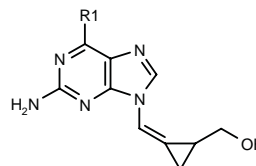
2(*S*)-[2-[(*Z*)-2-Amino-6-methoxy-9*H*-purin-9-ylmethylene]cyclopropylmethoxy(phenoxy)phosphorylamino]propionic acid methyl ester

(*Z*)-*N*-[2-(2-Amino-6-methoxypurin-9-ylmethylene)-cyclopropylmethoxy(phenoxy)phosphoryl]-L-alanine methyl ester



C21 H25 N6 O6 P; Mol wt: 488.4385

ACTION – Antiviral agent, a nucleoside analogue with significant antiviral activity against human and murine cytomegalovirus (HCMV, MCMV; $EC_{50} = 4.5$ and 0.24 μ M, respectively) at least comparable to ganciclovir ($EC_{50} = 2.3$ and 4.7 μ M, respectively). In a murine model of acute lethal MCMV infection, compound was as effective as ganciclovir at a dose of 40 mg/kg p.o. b.i.d. for 5 days, reducing mortality to 7% compared to 13% on ganciclovir at the same dose. Compound, although more toxic than ganciclovir *in vitro* in HFF cells ($CC_{50} = 33.3$ μ M vs. > 392 μ M) cells and moderately toxic in MEF cells ($CC_{50} = 126$ μ M), showed no toxicity in animals. Within this series of methylenecyclopropane nucleoside analogues, the following are also included:



Compound	R1	Formula
QYL-769 [263623]¹⁻⁴	cyclopropyl-NH	C ₁₃ H ₁₆ N ₆ O
QYL-941 [281959]³	OMe	C ₁₁ H ₁₃ N ₅ O ₂

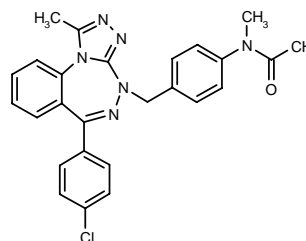
SOURCES – University of Alabama, Birmingham, AL (US); Wayne State University, Detroit, MI (US).

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- Hartline, C.B. et al. *In vitro* activity of methylenecyclopropane analogues of nucleosides against cytomegalovirus infections. Antivir Res 1998, 37(3): Abst 149.
- Qiu, Y.-L. et al. (*Z*)- And (*E*)-2-(hydroxymethylcyclopropylidene)methylpurines and pyrimidines as antiviral agents. Antivir Chem Chemother 1998, 9(4): 341.
- Rybak, R.J. et al. Effective treatment of murine cytomegalovirus infections with methylenecyclopropane analogues of nucleosides. Antivir Res 1999, 43(3): 175.
- Rybak, R.J. et al. Effective treatment of murine cytomegalovirus infections with methylenecyclopropane analogues of nucleosides. Antivir Res 1998, 37(3): Abst 150.

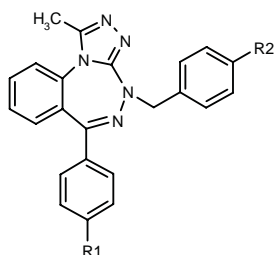
AIDS MEDICINES**282088**

N-[4-[6-(4-Chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,3,4]benzotriazepin-4-ylmethyl]phenyl]-*N*-methylacetamide



C26 H23 Cl N6 O; Mol wt: 470.9617

ACTION – An inhibitor of Fas-mediated apoptosis shown to inhibit cell viability in human T-cell HBP-ALL cells (IC_{50} = 0.02 μ M), as well as lipopolysaccharide-stimulated TNF- α production, concanavalin A (Con A)-stimulated IL-2 production and HIV-1 proliferation in human peripheral blood mononuclear cells (PBMCs; IC_{50} = 0.06, 0.5 and 0.25 μ M, respectively). In addition, compound was shown to inhibit Con A-stimulated increase in Fas ligand mRNA levels by 77% in spleen of mice treated with 10 mg/kg p.o. test compound. It was also effective in a murine model of Con A-induced hepatitis, as demonstrated by 63% inhibition of the increase in ALT (GPT) levels in plasma following oral administration of 10 mg/kg. Other exemplified compounds include the following:



Compound	R1	R2	Formula
282089	Cl	SO ₂ Me	C ₂₄ H ₂₀ ClN ₅ O ₂ S
282090	Cl	CON(Me) ₂	C ₂₆ H ₂₃ ClN ₆ O
282091	Cl	CON(Et) ₂	C ₂₈ H ₂₇ ClN ₆ O
282092	Cl	CON(Pr) ₂	C ₃₀ H ₃₁ ClN ₆ O
282093	Me	CONHMe	C ₂₆ H ₂₄ N ₆ O
282094	Cl	CONHMe	C ₂₅ H ₂₁ ClN ₆ O
282095	Cl	CONHPr	C ₂₇ H ₂₅ ClN ₆ O
282096	Cl	1,3,4-oxadiazol-2-yl	C ₂₅ H ₁₈ ClN ₇ O

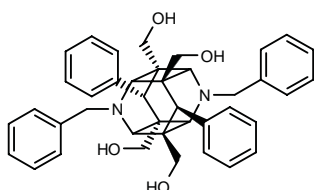
SOURCE – Japan Tobacco.

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1. Nakamura, T. et al. (Japan Tobacco Inc.) *Apoptosis inhibitors*. JP 1999228576.

282216

3,9-Dibenzyl-1,5,7,11-tetrahydroxymethyl-6,12-diphenyl-3,9-diazapentacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane



C40 H42 N2 O4; Mol wt: 614.7818

ACTION – Anti-HIV agent, a competitive, nonpeptide HIV-1 protease inhibitor (IC_{50} = 16.2 μ M; K_i = 7.8 μ M).

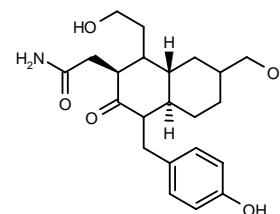
SOURCE – Novartis.

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283311

2-[(2S,4aR,8aS)-4-(4-Hydroxybenzyl)-1-(2-hydroxyethyl)-7-(hydroxymethyl)-3-oxoperhydronaphthalen-2-yl]-acetamide



C22 H31 N O5; Mol wt: 389.4889

ACTION – Antiviral agent for AIDS, a peptidomimetic designed to mimic the three-dimensional structure of peptide T that acts by binding T4 receptors, thereby inhibiting binding of HIV; it is reported to display a substantially longer half-life *in vivo* than peptide T.

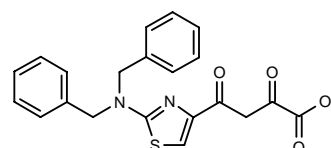
SOURCE – Innapharma.

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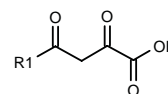
283935

4-[2-(Dibenzylamino)thiazol-4-yl]-2,4-dioxobutyric acid



C21 H18 N2 O4 S; Mol wt: 394.4492

ACTION – HIV Integrase inhibitor (IC_{50} < 1 μ M in assays for strand transfer activity of integrase catalyzed by recombinant integrase and preintegration complexes) shown to inhibit acute HIV infection in T-lymphocytes (IC_{95} < 10 μ M). Other specifically claimed sulfur-containing heteroaryl dioxo-butyric acid derivatives are:



Compound	R1	Formula
283936	3-(PhCH ₂ O)-2-thienyl	C ₁₅ H ₁₂ O ₅ S
283937	4-(4-Cl-PhS)-3-thienyl	C ₁₄ H ₉ ClO ₄ S ₂
283938	3-(4-F-PhCH ₂ O)-2-thienyl	C ₁₅ H ₁₁ FO ₅ S
283939	3-benzothieryl	C ₁₂ H ₈ O ₄ S
283940	2-benzothieryl	C ₁₂ H ₈ O ₄ S
283941	3-benzothieryl-CH ₂	C ₁₃ H ₁₀ O ₄ S
283942	4,5-dihydronaphtho[1,2-b]thien-3-yl	C ₁₆ H ₁₂ O ₄ S

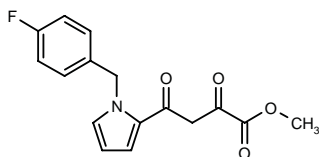
SOURCE – Merck & Co.

REFERENCES

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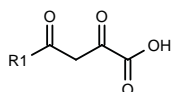
283999

4-[1-(4-Fluorobenzyl)-1*H*-pyrrol-2-yl]-2,4-dioxobutyric acid methyl ester



C₁₆H₁₄F N O₄; Mol wt: 303.2876

ACTION – Potent HIV integrase inhibitor with IC₅₀ values of below 1 μM in the integrase and preintegration complex assay, as well as IC₉₅ values of below 10 μM for inhibition of acute HIV infection in T-cells. Other specifically claimed nitrogen-containing heteroaryl dioxo-butyric acid derivatives are:



Compound	R1	Formula
284000	1-(3-Cl-PhCH2)-2-pyrrolyl	C ₁₅ H ₁₂ ClNO ₄
284001	1-(cyclopentyl-CH2)-2-pyrrolyl	C ₁₄ H ₁₇ NO ₄
284002	5-(PhCH2)-2-pyrrolyl	C ₁₅ H ₁₃ NO ₄
284003	1-(PhCH2)-3-pyrrolyl	C ₁₅ H ₁₃ NO ₄
284004	1-(4-F-PhCH2)-4-[PhCH2N(Me)]-2-pyrrolyl	C ₂₃ H ₂₁ FN ₂ O ₄
284005	1-(3-Cl-PhCH2)-3-Me-4-pyrazolyl	C ₁₅ H ₁₃ ClN ₂ O ₄
284006	1-(3-thienyl-CH2)-3-pyrrolyl	C ₁₃ H ₁₁ NO ₄ S
284007	4-(3-Cl-PhCH2)-1-Me-3-pyrrolyl	C ₁₆ H ₁₄ ClNO ₄

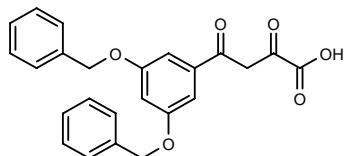
SOURCES – Merck & Co.; Tularik.

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1. Selnick, H.G. et al. (Merck & Co., Inc.;Tularik Inc.) *HIV integrase inhibitors*. WO 9962513.

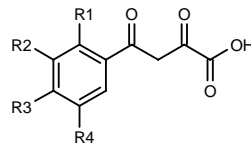
284453

4-[3,5-Bis(benzyloxy)phenyl]-2,4-dioxobutyric acid



C₂₄H₂₀O₆; Mol wt: 404.4160

ACTION – Antiviral agent for AIDS with HIV integrase-inhibitory activity. A representative compound from a series of 6-membered aromatic and heteroaromatic-dioxo-butyric acid derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
284454	OCH2Ph	H	H	H	C ₁₇ H ₁₄ O ₅
284455	i-PrO	H	H	CH2Ph	C ₂₀ H ₂₀ O ₅
284456	OMe	CH2N(Me) ₂	H	CH2Ph	C ₂₁ H ₂₃ NO ₅
284457	OCH2Ph	OMe	H	CH2Ph	C ₂₅ H ₂₂ O ₆
284458	OMe	OMe	OMe	CH2Ph	C ₂₆ H ₂₄ O ₇
284459	OMe	CH2OH	H	CH2Ph	C ₁₉ H ₁₈ O ₆
284460	OMe	t-BuNHCO	H	CH2Ph	C ₂₃ H ₂₅ NO ₆
284462	cyclopentyl-O	H	H	CH2Ph	C ₂₂ H ₂₂ O ₅
284463	H	H	-CH2CH2CH(Ph)-		C ₁₉ H ₁₆ O ₄
284464	i-PrO	1,2,4-triazol-1-yl	H	CH2Ph	C ₂₃ H ₂₃ N ₃ O ₅

SOURCES – Merck & Co.; Tularik.

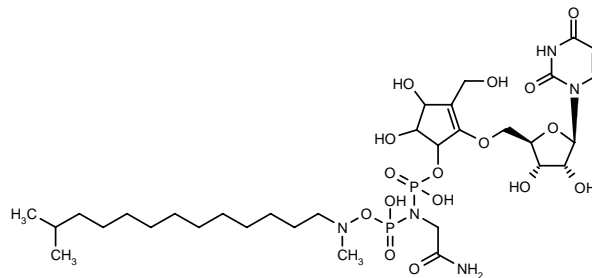
REFERENCES

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EM-2487

274807

5'-O-[5-[[N-(Carbamoylmethyl)-N-[hydroxy[N-methyl-N-(12-methyltridecyl)aminoxy]phosphoryl]amino]-(hydroxy)phosphoryloxy]-3,4-dihydroxy-2-(hydroxymethyl)-1-cyclopenten-1-yl]uridine



C₃₂H₅₇N₅O₁₆P₂; Mol wt: 829.7693

ACTION – Anti-HIV-1 agent extracted from the culture filtrate of *Streptomyces* sp. Mer-2487, with potent and selective activity against HIV-1 replication in both acutely and chronically infected cells (IC₅₀ = 0.075-2.1 μM) and no cytotoxic activity at effective concentrations. Compound showed inhibitory activity against a variety of HIV-1 strains and HIV-2 in acutely infected T-cell lines and could suppress TNF-α-induced HIV-1 production in latently infected cells (OM-10.1 and ACH-2), as well as constitutive viral production in chronically infected cells (MOLT-4/IIIB and U937/IIIB). It selectively prevented viral mRNA synthesis in acutely infected MOLT-4 cells and inhibited Tat-induced gene expression, without affecting basal or TNF-α-induced transcription, suggesting that HIV-1 inhibition occurs at the transcriptional level via inhibition of Tat function.

SOURCES – Eisai; Mercian.

REFERENCES

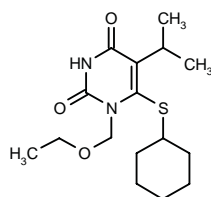
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2. Baba, M. et al. *Inhibition of human immunodeficiency virus type 1 replication in acutely and chronically infected cells by EM2487, a novel substance produced by a Streptomyces species*. Antimicrob Agents Chemother 1999, 43(10): 2350.
3. Baba, M. et al. *Potent and selective inhibition of HIV-1 replication by a novel Tat antagonist, EM2487, in acutely and chronically infected cells*. Antivir Res 1999, 41(2): Abst 28.
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TNK-6123²

281333

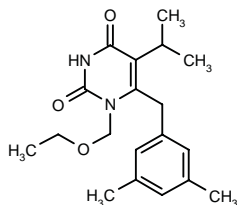
6-(Cyclohexylsulfanyl)-1-(ethoxymethyl)-5-isopropyl-1,3-dihydropyrimidine-2,4-dione

6-(Cyclohexylsulfanyl)-1-(ethoxymethyl)-5-isopropyluracil



C16 H26 N2 O3 S; Mol wt: 326.4584

ACTION – Non-nucleoside HIV-1 reverse transcriptase inhibitor, an analogue of emivirine* with increased anti-HIV-1 activity with respect to the latter against drug-resistant strains. Compound was active not only against wild-type HIV-1 strains (IC₅₀ = 3 nM against IIIB and NL4-3 HIV-1 strains) but also showed nanomolar activity against two drug-resistant strains containing single amino acid changes: Tyr181Cys and Lys103Asn (IC₅₀ = 270 and 250 nM for IIIB-R(Y181C) and NL4-3K103N HIV-1 strains, respectively). Another emivirine analogue is:



GCA-186 [281334]¹⁻⁶: C19 H26 N2 O3

SOURCES – Kagoshima University, Kagoshima (JP); Oxford University, Oxford (GB); Showa University, Tokyo (JP).

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2. Hopkins, A.L. et al. *Design of MKC-442 (emivirine) analogues with improved activity against drug-resistant HIV mutants*. J Med Chem 1999, 42(22): 4500.
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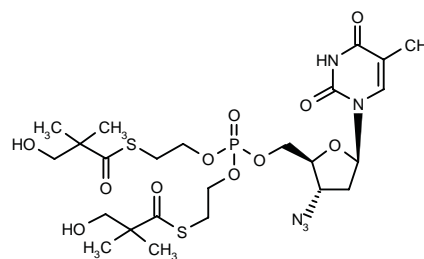
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*See **MKC-442** Drug Data Rep 1994, 016(01): 0099.

UA-926¹

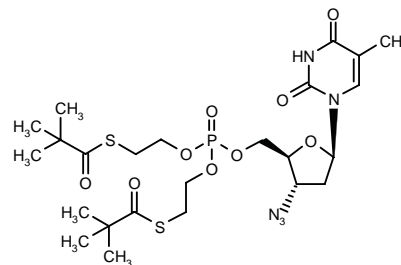
282497

3'-Azido-5'-O-[bis[2-[S-(3-hydroxy-2,2-dimethylpropionyl)sulfanyl]ethoxy]phosphoryl]-3'-deoxythymidine



C24 H38 N5 O11 P S2; Mol wt: 667.6942

ACTION – Anti-HIV agent, a bis(SATE)ester prodrug of zidovudine (AZT) monophosphate that, in an *in vitro* model of epithelial transport and uptake, was able to cross Caco-2 monolayers in intact form, indicating the feasibility of intracellular delivery of AZT monophosphate. Also, coadministration with Gelucire 44/14, a solubility/dissolution rate-enhancing agent, appeared to result in enhanced transport across the intestinal epithelium via inhibition of P-glycoprotein-related efflux systems. Another related compound is:



UA-428 [282495]¹⁻⁸: C24 H38 N5 O9 P S2

SOURCES – Katholieke Universiteit Leuven, Leuven (BE); Université Montpellier II, Montpellier (FR).

REFERENCES

1. Augustijns, P.F. et al. *Bis(SATE)ester prodrugs of AZT monophosphate: Selection of antiviral agent with the potential for oral absorption*. Annu Meet Am Assoc Pharm Sci (Nov 14-18, New Orleans) 1999, Abst 4186.
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3. Egron, D. et al. *Effect of the alkyl chain length on the anti-HIV efficiency of pronucleotides bearing S-acyl-thioalkyl phosphate protecting groups*. Bull Soc Chim Belg 1997, 106(7-8): 461.
4. Egron, D. et al. *Effect of the thioalkyl chain variation in the efficiency of SATE pronucleotide*. Nucleosides Nucleotides 1998, 17(9-11): 1725.

5. Lannuzel, M. et al. *Synthesis of the tBuSATE pronucleotide of AZT by two different synthetic approaches*. Nucleosides Nucleotides 1999, 18(4-5): 1001.

6. Lefebvre, I. et al. *Mononucleoside phosphotriester derivatives with S-acyl-2-thioethyl bioreversible phosphate-protecting groups: Intracellular delivery of 3'-azido-2',3'-dideoxythymidine 5'-monophosphate*. J Med Chem 1995, 38(20): 3941.

7. Lefebvre, I. et al. *Synthesis, decomposition pathways and "in vitro" evaluation of bioreversible phosphotriesters of AZT*. Nucleosides Nucleotides 1995, 14(3-5): 763.

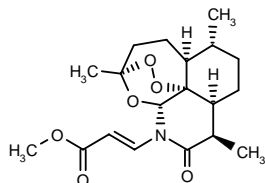
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TREATMENT OF PROTOZOAL DISEASES

282056

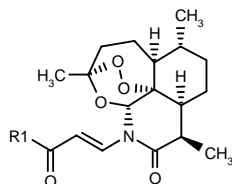
3-[(1*R*,4*S*,5*R*,8*S*,9*R*,12*R*,13*R*)-1,5,9-Trimethyl-10-oxo-14,15,16-trioxa-11-azatetracyclo[10.3.1.0^{4,13}.0^{8,13}]-hexadec-11-yl]prop-2(*E*)-enoic acid methyl ester

(3*R*,5*aS*,6*R*,8*aS*,9*R*,12*R*,12*aR*)-3-(3,6,9-Trimethyl-10-oxoperhydro-3,12-epoxy-1,2-dioxepino[4,3-*l*]isoquinolin-11-yl)-2(*E*)-propenoic acid methyl ester



C19 H27 N O6; Mol wt: 365.4233

ACTION – Antimalarial agent, an artemisinin derivative active against drug-resistant clones of *Plasmodium falciparum*; it was 2-fold more effective than artemisinin against the D-6 clone resistant to mefloquine but sensitive to chloroquine, quinine, sulfadoxine and pyrimethamine, and comparable to artemisinin against the W-2 clone resistant to chloroquine, quinine, sulfadoxine and pyrimethamine but sensitive to mefloquine. Other *N*-substituted 11-azaartemisinins include the following:



Compound	R1	Formula
282057	Me	C ₁₉ H ₂₇ NO ₅
282058	N(Me) ₂	C ₂₀ H ₃₀ N ₂ O ₅

SOURCES – National Institutes of Health, Bethesda, MD (US); Walter Reed Army Institute of Research, Washington, DC (US).

REFERENCES

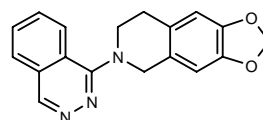
1. Katz, E. et al. *Structure and antimalarial activity of adducts of 11-azaartemisinin with conjugated terminal acetylenes*. Bioorg Med Chem Lett 1999, 9(20): 2969.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

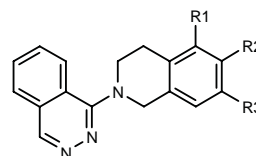
282006

6-(1-Phthalazinyl)-5,6,7,8-tetrahydro-1,3-dioxolo[4,5-*g*]-isoquinoline



C18 H15 N3 O2; Mol wt: 305.3355

ACTION – An inhibitor of the production of TNF- α (IC₅₀ = 3 μ M in lipopolysaccharide-stimulated murine peritoneal macrophages), with potential in the treatment of shock, cachexia, multiple organ failure, chronic rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, osteoarthritis, Behcet's disease, systemic lupus erythematosus, graft-versus-host disease, malaria, AIDS, hepatitis, meningitis and type II diabetes. Within this series of tetrahydroisoquinolinylphthalazine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
282007	H	H	H	C ₁₇ H ₁₅ N ₃
282008	H	OMe	H	C ₁₈ H ₁₇ N ₃ O
282009	H	OMe	OMe	C ₁₉ H ₁₉ N ₃ O ₂
282010	OMe	OMe	OMe	C ₂₀ H ₂₁ N ₃ O ₃
282011	H	Cl	Cl	C ₁₇ H ₁₃ Cl ₂ N ₃
282012	Cl	Cl	H	C ₁₇ H ₁₃ Cl ₂ N ₃

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Fujita, K. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Tetrahydroisoquinolinyl phthalazine derivs*. JP 1999222486.

5. Lannuzel, M. et al. *Synthesis of the tBuSATE pronucleotide of AZT by two different synthetic approaches*. Nucleosides Nucleotides 1999, 18(4-5): 1001.

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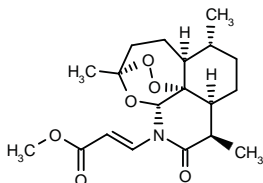
8. Thumann-Schweitzer, C. et al. *Anti-human immunodeficiency virus type 1 activities of dideoxynucleoside phosphotriester derivatives in primary monocytes/macrophages*. Res Virol 1996, 147(2-3): 155.

TREATMENT OF PROTOZOAL DISEASES

282056

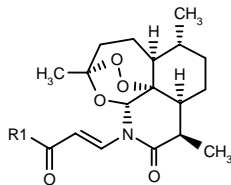
3-[(1*R*,4*S*,5*R*,8*S*,9*R*,12*R*,13*R*)-1,5,9-Trimethyl-10-oxo-14,15,16-trioxa-11-azatetracyclo[10.3.1.0^{4,13}.0^{8,13}]-hexadec-11-yl]prop-2(*E*)-enoic acid methyl ester

(3*R*,5*aS*,6*R*,8*aS*,9*R*,12*R*,12*aR*)-3-(3,6,9-Trimethyl-10-oxoperhydro-3,12-epoxy-1,2-dioxepino[4,3-*l*]isoquinolin-11-yl)-2(*E*)-propenoic acid methyl ester



C19 H27 N O6; Mol wt: 365.4233

ACTION – Antimalarial agent, an artemisinin derivative active against drug-resistant clones of *Plasmodium falciparum*; it was 2-fold more effective than artemisinin against the D-6 clone resistant to mefloquine but sensitive to chloroquine, quinine, sulfadoxine and pyrimethamine, and comparable to artemisinin against the W-2 clone resistant to chloroquine, quinine, sulfadoxine and pyrimethamine but sensitive to mefloquine. Other *N*-substituted 11-azaartemisinins include the following:



Compound	R1	Formula
282057	Me	C ₁₉ H ₂₇ NO ₅
282058	N(Me) ₂	C ₂₀ H ₃₀ N ₂ O ₅

SOURCES – National Institutes of Health, Bethesda, MD (US); Walter Reed Army Institute of Research, Washington, DC (US).

REFERENCES

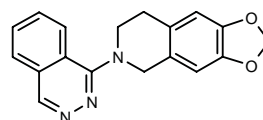
1. Katz, E. et al. *Structure and antimalarial activity of adducts of 11-azaartemisinin with conjugated terminal acetylenes*. Bioorg Med Chem Lett 1999, 9(20): 2969.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

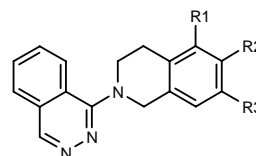
282006

6-(1-Phthalazinyl)-5,6,7,8-tetrahydro-1,3-dioxolo[4,5-*g*]-isoquinoline



C18 H15 N3 O2; Mol wt: 305.3355

ACTION – An inhibitor of the production of TNF- α (IC₅₀ = 3 μ M in lipopolysaccharide-stimulated murine peritoneal macrophages), with potential in the treatment of shock, cachexia, multiple organ failure, chronic rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, osteoarthritis, Behcet's disease, systemic lupus erythematosus, graft-versus-host disease, malaria, AIDS, hepatitis, meningitis and type II diabetes. Within this series of tetrahydroisoquinolinylphthalazine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
282007	H	H	H	C ₁₇ H ₁₅ N ₃
282008	H	OMe	H	C ₁₈ H ₁₇ N ₃ O
282009	H	OMe	OMe	C ₁₉ H ₁₉ N ₃ O ₂
282010	OMe	OMe	OMe	C ₂₀ H ₂₁ N ₃ O ₃
282011	H	Cl	Cl	C ₁₇ H ₁₃ Cl ₂ N ₃
282012	Cl	Cl	H	C ₁₇ H ₁₃ Cl ₂ N ₃

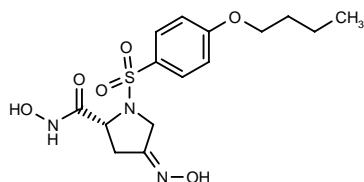
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Fujita, K. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Tetrahydroisoquinolinyl phthalazine derivs*. JP 1999222486.

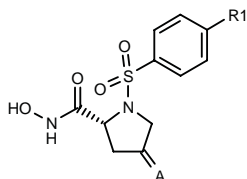
282183

1-(4-Butoxyphenylsulfonyl)-4-(hydroxyimino)pyrrolidine-2(*R*)-carboxylic acid



C15 H21 N3 O6 S; Mol wt: 371.4119

ACTION – Matrix metalloproteinase inhibitor with potential in the treatment of arthritis, cancer, multiple sclerosis, cardiovascular disorders, skin disorders, ocular disorders, inflammation, musculoskeletal disease, cachexia and gum disease. Within this series of substituted pyrrolidine hydroxamate derivatives, the following are also included:



Compound	R1	A	Formula
282185	OMe	-N(OMe)-	C ₁₃ H ₁₇ N ₃ O ₆ S
282187	OBu	-N(OMe)-	C ₁₆ H ₂₃ N ₃ O ₆ S
282188	4-Pyr-O	-N(OMe)-	C ₁₇ H ₁₈ N ₄ O ₆ S
282189	OBu	-N(1-Pip)-	C ₂₀ H ₃₀ N ₄ O ₅ S
282190	OPr	-N[CH ₂ Ph] ₂ -	C ₂₈ H ₃₂ N ₄ O ₅ S
282199	Me	-CH ₂ -	C ₁₃ H ₁₆ N ₂ O ₄ S
282201	NO ₂	-N(1-pyrrolyl)-	C ₁₅ H ₁₅ N ₅ O ₆ S
282203	OMe	-cyclopentylidene-	C ₁₇ H ₂₂ N ₂ O ₅ S

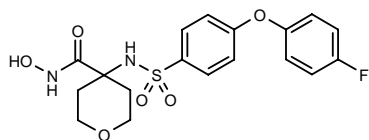
SOURCE – Procter & Gamble.

REFERENCES

1. Cheng, M. et al. (The Procter & Gamble Co.) *Subst. pyrrolidine hydroxamate metalloproteinase inhibitors*. WO 9952868.

282232

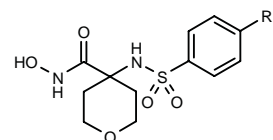
4-[4-(4-Fluorophenoxy)phenylsulfonylamido]tetrahydropyran-4-carboxylic acid



C18 H19 F N2 O6 S; Mol wt: 410.4201

ACTION – Matrix metalloproteinase (MMP) inhibitor that selectively inhibits MMP-13 (collagenase 3) and/or TNF- α -converting enzyme (TACE) with respect to MMP-1 (fibroblast collagenase); it is at least 100-fold less potent against recombinant human MMP-1 than against TACE. Potentially useful in the treatment of a wide variety of disorders including osteoarthritis and rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmo-

nary disease, Alzheimer's disease, restenosis, osteoporosis, atherosclerosis, stroke, etc. Other specifically claimed (4-arylsulfonylamino)-tetrahydropyran-4-carboxylic acid hydroxamides are:



Compound	R1	Formula
282233	4-Cl-PhO	C ₁₈ H ₁₉ ClN ₂ O ₆ S
282234	OPh	C ₁₈ H ₂₀ N ₂ O ₆ S
282235	4-Pyr-O	C ₁₇ H ₁₉ N ₃ O ₆ S
282236	4-F-Ph	C ₁₈ H ₁₉ FN ₂ O ₆ S
282237	4-F-PhCH ₂ O	C ₁₉ H ₂₁ FN ₂ O ₆ S
282238	OCH ₂ Ph	C ₁₉ H ₂₂ N ₂ O ₆ S
282239	4-F-PhCH ₂ CH ₂ O	C ₂₀ H ₂₃ FN ₂ O ₆ S

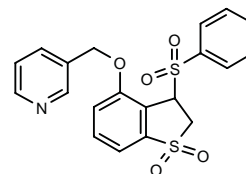
SOURCE – Pfizer.

REFERENCES

1. Reiter, L.A. (Pfizer Products Inc.) *(4-Arylsulfonylamino)-tetrahydropyran-4-carboxylic acid hydroxamides*. WO 9952889.

282763

3-(Phenylsulfonyl)-4-(3-pyridinylmethoxy)-2,3-dihydrobenzo[*b*]thiophene *S,S*-dioxide



C20 H17 N O5 S₂; Mol wt: 415.4883

ACTION – IL-6 and IL-12 production inhibitor found to inhibit TNF- α -stimulated IL-6 production in human lung tumor A549 cells with an IC₅₀ of 4.4 μ M and no cytotoxicity at up to 10 μ M, and to inhibit interferon gamma-stimulated IL-12 production in human peripheral blood monocytes with an IC₅₀ of 0.11 μ M and no cytotoxicity at up to 1 μ M. Potentially useful in the treatment or prevention of inflammatory disorders, chronic rheumatoid arthritis, sepsis, cancers such as multiple myeloma, renal cell cancer and Kaposi's sarcoma, osteoporosis, cachexia, psoriasis, nephritis, hypergammaglobulinemia, diabetes, autoimmune diseases, hepatitis, multiple sclerosis, inflammatory bowel disease, graft-versus-host disease and infectious diseases.

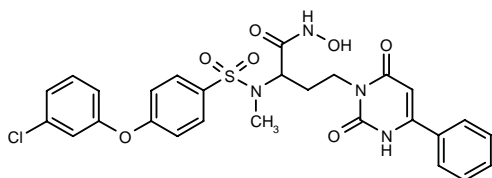
SOURCE – Ono.

REFERENCES

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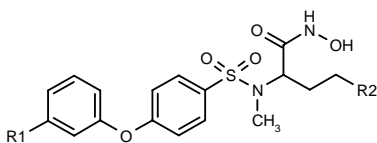
282841

2-[N-[4-(3-Chlorophenoxy)phenyl]-N-methylsulfonamido]-4-(2,6-dioxo-4-phenyl-1,2,3,6-tetrahydropyrimidin-1-yl)butyroxamic acid



C27 H25 Cl N4 O7 S; Mol wt: 585.0345

ACTION – Matrix metalloproteinase (MMP) inhibitor active against MMP-13 (collagenase 3) and aggrecanase; it inhibited MMP-13 from human chondrosarcoma cells with an IC_{50} of 0.32 nM and aggrecanase from bovine nasal septal cartilage with an IC_{50} of 2.2 nM. Other exemplified sulfonamide derivatives are:



Compound	R1	R2	Formula
282842	H	2,4-dioxo-1,2,3,4-tetrahydro-thieno[3,2-d]pyrimidin-3-yl	$C_{23}H_{22}N_4O_7S_2$
282843	Cl	2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl	$C_{25}H_{23}ClN_4O_7S$

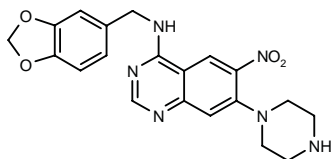
SOURCE – Sankyo.

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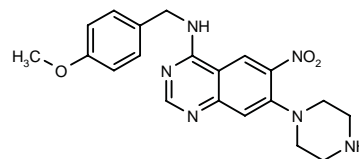
282983

N-(1,3-Benzodioxol-5-ylmethyl)-N-[6-nitro-7-(1-piperazinyl)quinazolin-4-yl]amine



C20 H20 N6 O4; Mol wt: 408.4160

ACTION – An inhibitor of TNF- α production (IC_{50} = 0.08 μ M against lipopolysaccharide-induced TNF- α production in human peripheral blood mononuclear cells) shown to inhibit concanavalin A-induced T-cell proliferation (IC_{50} = 0.8 μ M). Potentially useful for the treatment of rheumatoid arthritis. Another representative 6-nitroquinazoline derivative is:



282984: C20 H22 N6 O3

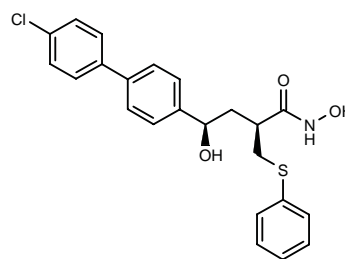
SOURCE – Japan Energy.

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1. Tobe, M. et al. *Synthesis and structure-activity relationship of 6-nitroquinazoline derivatives for inhibitory action of TNF- α production.* 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 1P-09.

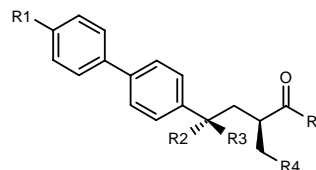
283832

4(R)-(4'-Chlorobiphenyl-4-yl)-4-hydroxy-2(S)-(phenylsulfanylmethyl)butyroxamic acid

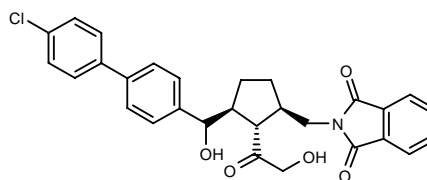


C23 H22 Cl N O3 S; Mol wt: 427.9498

ACTION – Matrix metalloproteinase (MMP) inhibitor for the treatment of a wide range of disorders including osteoarthritis, rheumatoid arthritis, osteoporosis, chronic obstructive pulmonary disease, stroke, Alzheimer's disease, atherosclerosis, cachexia, septic shock and inflammatory bowel disease. A representative compound from a series of substituted 4-biarylbutyric and 5-biarylpentanoic acid derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
283833	Cl	OH	H	SPh	NHOH	$C_{23}H_{22}ClNO_3S$
283834	Cl	H	OH	SPh	NHSO2Me	$C_{24}H_{24}ClNO_4S_2$
283835	Cl	OH	H	SPh	NHSO2Me	$C_{24}H_{24}ClNO_4S_2$
283837	Cl	-O-		SPh	NHSO2Me	$C_{24}H_{22}ClNO_4S_2$
283838	Br	-O-		CH2CH2Ph	CH2OH	$C_{26}H_{25}BrO_3$
283840	Br	-O-		CH2CH2Ph	NHOH	$C_{26}H_{24}BrNO_3$
283865	Cl	H	OH	SPh	CH2OH	$C_{24}H_{23}ClO_3S$
283866	Cl	OH	H	SPh	CH2OH	$C_{24}H_{23}ClO_3S$



283842: C29 H26 Cl N O5

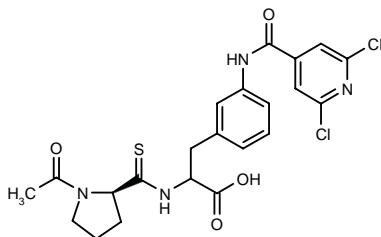
SOURCE – Bayer.

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1. Kluender, H.C.E. et al. (Bayer Corp.) *Subst. 4-biarylbutyric and 5-biarylpentanoic acid derivs. as matrix metalloprotease inhibitors*. WO 9961413.

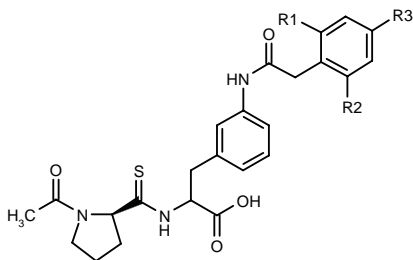
283890

N-(Acetyl-D-thiopropyl)-3-(2,6-dichloropyridin-4-ylcarboxamido)-DL-phenylalanine

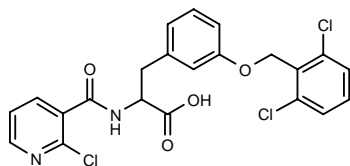


C22 H22 Cl2 N4 O4 S; Mol wt: 509.4118

ACTION – Potent and selective α_4 integrin inhibitor that inhibits $\alpha_4\beta_1$ and/or $\alpha_4\beta_7$ integrins at concentrations with little or no inhibitory activity against other α integrin subtypes. Potentially useful in immune and inflammatory disorders, particularly rheumatoid arthritis, vasculitis, multiple sclerosis, allograft rejection, diabetes, psoriasis, dermatitis, asthma and inflammatory bowel disease. Other specifically claimed phenylalanine derivatives are:



Compound	R1	R2	R3	Formula
283891	H	H	OMe	C ₂₅ H ₂₉ N ₃ O ₅ S
283892	Cl	Cl	H	C ₂₄ H ₂₅ Cl ₂ N ₃ O ₄ S



283893: C22 H17 Cl3 N2 O4

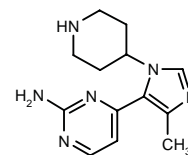
SOURCE – Celltech Chiroscience (Celltech Group).

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283895

4-[4-Methyl-1-(4-piperidiny)-1H-imidazol-5-yl]pyrimidin-2-ylamine



C13 H18 N6; Mol wt: 258.3272

ACTION – ERK (extracellular signal-regulated kinase)/MAP (mitogen-activated protein) kinase inhibitor with potential in the treatment of ERK/MAP kinase-mediated diseases including psoriatic arthritis, rheumatoid arthritis, osteoarthritis, septic shock, Alzheimer's disease, stroke, asthma, adult respiratory distress syndrome, cerebral malaria, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, inflammatory bowel disease, transplant rejection, multiple sclerosis and psoriasis.

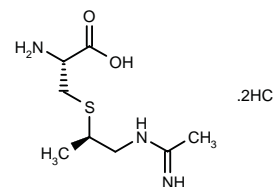
SOURCE – SmithKline Beecham.

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1. Adams, J.L. (SmithKline Beecham Corp.) *Novel subst. imidazole cpds*. WO 9961440.

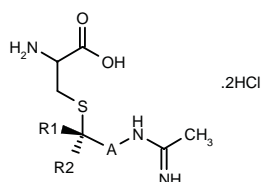
284029

S-[2-(1-Iminoethylamino)-1(R)-methylethyl]-L-cysteine dihydrochloride



C8 H17 N3 O2 S . 2HCl; Mol wt: 292.2291

ACTION – Selective inhibitor of inducible nitric oxide synthase (iNOS) giving an IC₅₀ of 2.0 μ M for inhibition of purified human iNOS and an IC₅₀ of 0.26 μ M for inhibition of enzyme activity in rat aortic rings versus an IC₅₀ of 20 μ M for endothelial NOS (eNOS) in this preparation; in addition, no inhibition of neuronal NOS (nNOS) was seen in rat brain slices at concentrations of up to 80 μ M. It showed an oral bioavailability of over 90% and a half-life of 2-4 h in rats given a dose of 50 mg/kg p.o. Potentially useful in the treatment or prophylaxis of arthritis, asthma, ileus and migraine. Other exemplified amidino compounds are:



Compound	R1	R2	A	Isomer	Formula
284030	H	H	CH ₂	L	C ₈ H ₁₇ N ₃ O ₂ S.2HCl
284031	H	H	CH ₂	D	C ₈ H ₁₇ N ₃ O ₂ S.2HCl
284032	Me	Me	CH ₂	D	C ₈ H ₁₇ N ₃ O ₂ S.2HCl
284033	H,cyclopropyl-CH ₂	bond	bond	L	C ₁₀ H ₁₉ N ₃ O ₂ S.2HCl

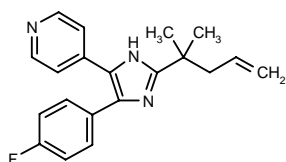
SOURCE – Glaxo Wellcome.

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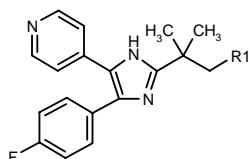
284046

4-[2-(1,1-Dimethyl-3-butenyl)-4-(4-fluorophenyl)-1H-imidazol-5-yl]pyridine



C₂₀ H₂₀ F N₃; Mol wt: 321.3970

ACTION – Cytokine production inhibitor that acts through inhibition of p38/CSBP/RK kinase (IC₅₀ < 50 μM). In particular, it is useful in the prophylaxis of diseases exacerbated or caused by excessive or unregulated IL-1, IL-6, IL-8 or TNF production such as psoriatic arthritis, rheumatoid arthritis, osteoarthritis, septic shock, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, osteoporosis, restenosis, congestive heart failure, diabetes, allograft rejection, inflammatory bowel disease, ulcerative colitis, multiple sclerosis, contact dermatitis and psoriasis, as well as rhinovirus infection. Other specifically claimed 2-alkyl-substituted imidazole compounds are:



Compound	R1	Isomer	Formula
284047	N(Me)COPh		C ₂₆ H ₂₅ FN ₄ O
284048	CH(OH)CH ₂ OH	racemic	C ₂₀ H ₂₂ FN ₃ O ₂
284049	CO ₂ H		C ₁₉ H ₁₈ FN ₃ O ₂

SOURCE – SmithKline Beecham.

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1. Adams, J.L. and Lee, D. (SmithKline Beecham Corp.) *Novel 2-alkyl subst. imidazole cpds*. WO 9961437.

ANERGIX®-RA

282590

*Complex of the solubilized class II MHC molecule HLA-DRB1*0401 together with a specific 13-mer peptide (CDP263) derived from the human cartilage glycoprotein 39 (HCgp-39)*

AG-4263

ACTION – Agent for the treatment of rheumatoid arthritis, a soluble complex of native HLA-DR4 and a synthetic 13-mer peptide (CDP263) derived from human cartilage glycoprotein 39 (HCgp-39), proven to inhibit the development of and/or reduce autoimmune disease via induction of T-cell unresponsiveness, or anergy. Interim results from 19 patients in a randomized, double-blind, placebo-controlled, dose-escalation phase I study evaluating combined AG-4263/methotrexate demonstrated that compound is safe and well tolerated, does not induce immunogenicity or generalized immunosuppression, and has considerable clinical activity at the two highest dose levels.

SOURCES – Corixa; Organon.

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- Company Profile: Anergen*. DailyDrugNews.com (Daily Essentials) 1998, Feb 16.
- Organon team identifies rheumatoid arthritis-related antigen*. DailyDrugNews.com (Daily Essentials) 1997, June 5.

HCL-113

285051

21-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-CATTACTCAAAGCCACGGTAA-3'

HCL-102R2

ACTION – Antisense oligonucleotide targeted to IL-15 and capable of downregulating its expression, proven to inhibit IL-15 production to about 16% of control at concentrations as low as 0.1 μM. Potentially useful in the treatment of rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, chronic liver disease (cirrhosis), ulcerative colitis and cell proliferative disorders.

SOURCE – Hisamitsu.

REFERENCES

1. Veerapanane, D. et al. (Hisamitsu Pharmaceutical Co., Ltd.) *Antisense oligonucleotide targeted to IL-15*. WO 0001851.

INFLIXIMAB⁺

Prop INN

New indication

198460

Immunoglobulin G (human–mouse monoclonal cA2 heavy chain anti-human tumor necrosis factor), disulfide with human–mouse monoclonal cA2 light chain, dimer

AvakineTM (former brand name)

cA2

CentTNF[®]

TA-650

ACTION – Chimeric monoclonal antibody to TNF- α .

INDICATION – In combination with methotrexate, for reducing the signs and symptoms of rheumatoid arthritis in patients who do not respond to methotrexate alone.

PRESENTATION – Vials (20 ml, single-use) of lyophilized concentrate for i.v. injection, 100 mg.

PROPRIETARY NAME – Remicade (US).

SOURCE – Centocor.

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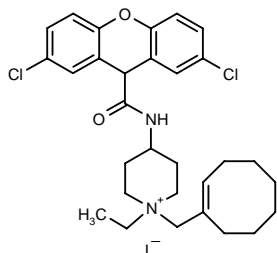
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*Drug Data Rep 1998, 020(11): 0957

J-113863

282962

1-(1-Cycloocten-1-ylmethyl)-4-(chloroxanthen-9-yl-carboxamido)-1-ethylpiperidinium iodide



C30 H37 Cl2 I N2 O2; Mol wt: 655.4403

ACTION – Potent, nonpeptide chemokine CCR1 receptor antagonist able to inhibit [125 I]-MIP-1 α binding to both human and mouse CCR1 receptors with IC₅₀ values of 0.9 and 5.8 nM, respectively. Potentially useful as a tool to elucidate the pathophysiological role of CCR1 receptors in chronic inflammatory diseases, as well as for the treatment of the latter.

SOURCE – Banyu.

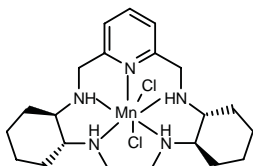
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M-40403

281618

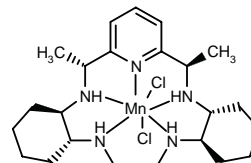
Dichloro[(4a*R*,13a*R*,17a*R*,21a*R*)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-eicosahydro-1,7-nitrilo-7*H*-dibenzo[*b,h*][1,4,7,10]tetraazacycloheptadecine- κ N⁵, κ N¹³, κ N¹⁸, κ N²¹, κ N²²]manganese



C21 H35 Cl2 Mn N5; Mol wt: 483.3865

ACTION – Antiinflammatory agent, a nonpeptide manganese-based superoxide dismutase (SOD) mimetic that is much more stable and more active than natural SOD. In a rat model of inflammation (carrageenan-induced paw edema), compound at doses of 1-10 mg/kg i.v. produced marked inhibition of paw edema, proinflammatory mediator (TNF- α , PGE₂ and IL-1 β) release, neutrophil infiltration and tissue damage (measured as lactate dehydrogenase release). In addition, at very low doses (0.1-1 mg/kg i.v.), it significantly increased survival in a rat model of severe shock induced by reperfusion damage to the gut and intestine (splanchnic artery occlusion). Potentially useful for the treatment of acute and chronic inflammation, as well as

reperfusion injury such as acute myocardial infarction or stroke. A structural analogue with no SOD activity was ineffective in these assays:



M-40404 [281619]: C23 H39 Cl2 Mn N5

SOURCES – MetaPhore; Searle (Pharmacia).

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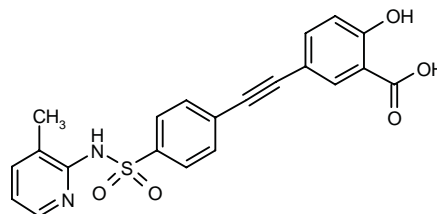
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SUSALIMOD*

Prop INN

223587

2-Hydroxy-5-[4-[*N*-(3-methyl-2-pyridyl)sulfamoyl]phenyl]ethynyl]benzoic acid



C21 H16 N2 O5 S; Mol wt: 408.4360

ACTION – Immunomodulating agent, a metabolically stable analogue of sulfasalazine for the treatment of autoimmune diseases such as ulcerative colitis and rheumatoid arthritis. Pharmacokinetic studies in various animal species and in man after i.v. administration showed that compound is excreted approximately 90% unchanged in bile and exhibited a much slower elimination rate in man compared with animals ($t_{1/2}$ = 16 and 0.5 h in man and animals, respectively). It was shown to reduce lipopolysaccharide-stimulated TNF- α levels in mouse serum in a concentration-dependent fashion, with an estimated IC₅₀ of 293 μ M.

SOURCE – Pharmacia & Upjohn (Pharmacia).

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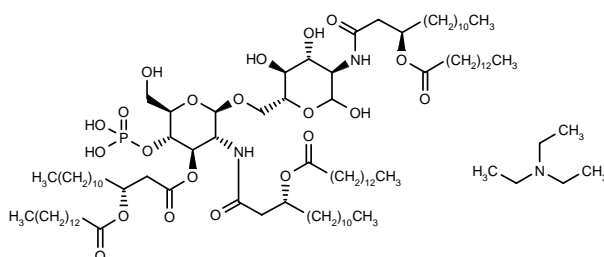
6. Proposed international nonproprietary names: List No. 73. WHO Drug Inf 1995, 9(2): 98.

*Identified compound **223587** Drug Data Rep 1995, 017(09): 0829.

IMMUNOMODULATING AGENTS

282192^{1,2}

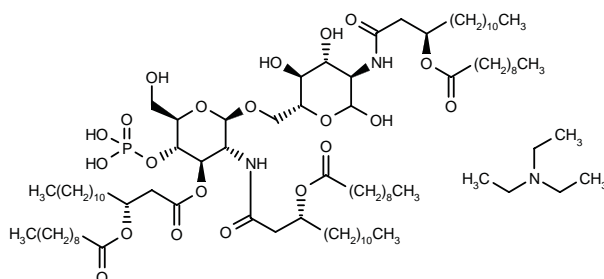
2-Deoxy-6-*O*-[2-deoxy-4-*O*-phosphono-3-*O*-[3(*R*)-(tetradecanoyloxy)tetradecanoyl]-2-[3(*R*)-(tetradecanoyloxy)tetradecanamido-β-D-glucopyranosyl]-2-[3(*R*)-(tetradecanoyloxy)tetradecanamido]-D-glucopyranose triethylammonium salt



C96 H181 N2 O21 P . C6 H15 N; Mol wt: 1831.6440

M.p. 192-4 °C; $[\alpha]_D^{25} +3.2^\circ$ (*c* 0.72, CHCl₃).

ACTION – Immunostimulant, a derivative of monophosphoryl lipid A (MPL) proven to induce inducible nitric oxide synthase (iNOS) gene expression in murine macrophages (ED₅₀ = 5 ng/ml) and the *ex vivo* production of proinflammatory cytokines (TNF-α and IL-1β) in human peripheral monocytes. Potent adjuvant activity was demonstrated in a murine model, where it was able to induce high tetanus toxoid-specific antibody titers. When compared to MPL, compound showed less activity for iNOS induction but better adjuvant activity. In addition, it displayed 50- and 250-fold lower toxicity than MPL, measured as lethal toxicity in D-galactosamine-treated mice and pyrogenicity in rabbits. Another MPL derivative selected for further evaluation is:



282191¹: C84 H157 N2 O21 P . C6 H15 N

SOURCE – Corixa.

REFERENCES

- Johnson, D.A. et al. 3-*O*-Desacyl monophosphoryl lipid A derivatives: Synthesis and immunostimulant activities. *J Med Chem* 1999, 42(22): 4640.
- Johnson, D.A. et al. Chemical synthesis of the major constituents of *Salmonella minnesota* monophosphoryl lipid A. *J Carbohydr Chem* 1998, 17(9): 1421.

283312

L-Seryl-L-threonyl-L-isoleucyl-L-leucyl-L-glutamyl-L-aspartyl-L-tryptophyl-L-asparaginyl-L-phenylalanyl-glycyl-L-leucyl-L-L-glutamyl-L-prolyl-L-prolyl-L-prolyl-glycyl-glycyl-L-threonyl-L-leucyl-L-glutamic acid

C99 H147 N23 O32; Mol wt: 2171.3790

ACTION – Peptide derived from the L1 open reading frame (ORF) of human papillomavirus type 16 (HPV16) capsid, for use in immunogenic compositions either coupled to a carrier or in multimer form. Compound was shown to produce identical titers against the immunizing peptide and against HPV16. Other compounds from this series of peptides derived from L1 and L2 ORFs of HPV16 include the following:

L-Prolyl-L-seryl-L-glutamyl-L-alanyl-L-threonyl-L-valyl-L-tyrosyl-L-leucyl-L-prolyl-L-prolyl-L-valyl-L-prolyl-L-valyl-L-seryl-L-lysyl-L-valyl-L-valyl-L-seryl-L-threonyl-L-aspartic acid

283313: C95 H153 N21 O31

L-Lysyl-glycyl-L-seryl-L-prolyl-L-cysteinyl-L-threonyl-L-asparaginyl-L-valyl-L-alanyl-L-valyl-L-asparaginyl-L-prolyl-glycyl-L-aspartyl-L-cysteinyl-L-prolyl-L-prolyl-L-leucyl-L-glutamyl-L-leucine

283314: C85 H139 N23 O29 S2

L-Phenylalanyl-L-asparaginyl-L-arginyl-L-alanyl-glycyl-L-threonyl-L-valyl-glycyl-L-glutamyl-L-asparaginyl-L-valyl-L-prolyl-L-aspartyl-L-aspartyl-L-leucyl-L-tyrosyl-L-isoleucyl-L-lysyl-glycyl-L-serine

283315: C94 H146 N26 O32

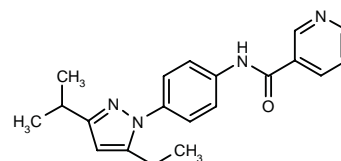
SOURCE – Euro-Diagnostica.

REFERENCES

- Dillner, J. (Euro-Diagnostica AB) Peptide-based compsn. against papillomavirus infection. US 5989548, WO 9633737.

283932

N-[4-(5-Ethyl-3-isopropyl-1*H*-pyrazol-1-yl)phenyl]pyridine-3-carboxamide



C20 H22 N4 O; Mol wt: 334.4208

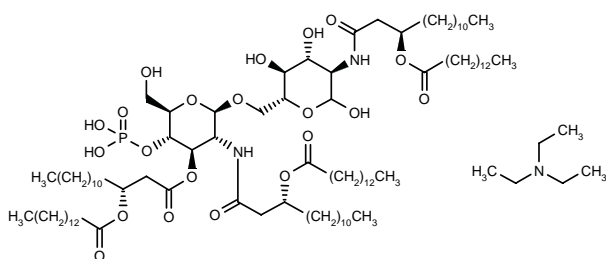
6. Proposed international nonproprietary names: List No. 73. WHO Drug Inf 1995, 9(2): 98.

*Identified compound **223587** Drug Data Rep 1995, 017(09): 0829.

IMMUNOMODULATING AGENTS

282192^{1,2}

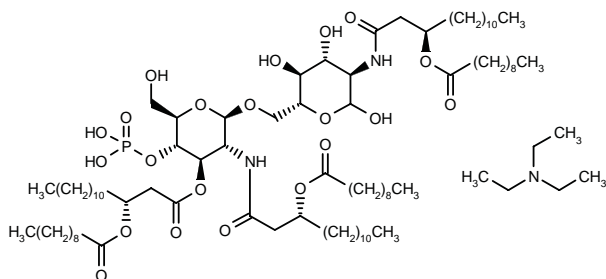
2-Deoxy-6-O-[2-deoxy-4-O-phosphono-3-O-[3(R)-(tetradecanoyloxy)tetradecanoyl]-2-[3(R)-(tetradecanoyloxy)tetradecanamido-β-D-glucopyranosyl]-2-[3(R)-(tetradecanoyloxy)tetradecanamido]-D-glucopyranose triethylammonium salt



C96 H181 N2 O21 P . C6 H15 N; Mol wt: 1831.6440

M.p. 192-4 °C; $[\alpha]_D^{25} +3.2^\circ$ (c 0.72, CHCl₃).

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SOURCE – Corixa.

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- Johnson, D.A. et al. 3-O-Desacyl monophosphoryl lipid A derivatives: Synthesis and immunostimulant activities. J Med Chem 1999, 42(22): 4640.
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283312

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283313: C95 H153 N21 O31

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283314: C85 H139 N23 O29 S2

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283315: C94 H146 N26 O32

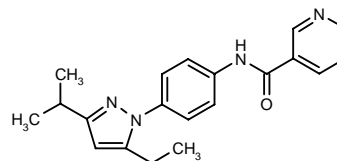
SOURCE – Euro-Diagnostica.

REFERENCES

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283932

N-[4-(5-Ethyl-3-isopropyl-1H-pyrazol-1-yl)phenyl]pyridine-3-carboxamide



C20 H22 N4 O; Mol wt: 334.4208

ACTION – Immunomodulating and antiinflammatory agent that acts by inhibiting IL-2 production in T-lymphocytes. It inhibited luciferase activity in an IL-2 promoter assay measuring transcriptional activation of a luciferase reporter gene with IC_{50} values below 10 μ M, and it is also reported to inhibit IL-2 production in stimulated human peripheral blood cells at similar concentrations. Furthermore, the compound inhibited the allogeneic cell transplant response in C57B1/6 mice to lymphocytes from the histoincompatible DBA strain by 74% at a dose of 100 mg/kg p.o. b.i.d. Particularly useful for preventing and treating immune disorders including organ transplant rejection, autoimmune diseases and inflammatory disorders.

SOURCE – Boehringer Ingelheim.

REFERENCES

1. Betageri, R. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Subst. 1-(4-aminophenyl)pyrroles and their use as antiinflammatory agents*. WO 9962885.

NmB/NmC/MF-59

283816

Combination vaccine for Neisseria meningitidis comprising outer membrane proteins from serogroup B (NmB), and oligosaccharides from serogroup C (NmC) in the presence of MF-59 as adjuvant.

ACTION – Combination vaccine for *Neisseria meningitidis* that induces an immune response to both serogroups B (NmB) and C (NmC), eliciting high titers of serum bactericidal antibody for both NmB and NmC, as demonstrated in guinea pigs.

SOURCE – Chiron.

REFERENCES

1. Granoff, D.M. et al. (Chiron Corp.) *Combination meningitidis B/C vaccines*. WO 9961053.

ONCOLYTIC DRUGS

ANTIMETABOLITES

AS-II-626-20

283749

20-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is: 5'-GGCTAAATCGCTCCACCAAG-3'

ACTION – Antisense phosphorothioate oligonucleotide that is directed against ribonucleotide reductase dimeric protein component R2, the aberrant expression of which has been found to cooperate with *ras* pathways, as well as to result in increased resistance of neoplastic cells to chemotherapeutic agents. Compound significantly decreased R2 protein levels in murine L60 tumor cells at a concentration of 0.2 μ M and was shown to be cytotoxic

against a variety of human tumor cell lines at this concentration. In addition, treatment of the highly malignant r-3 cell line with 0.2 μ M of compound markedly reduced the metastatic potential of these cells subsequently injected into C3H/HeN syngeneic mice. Potentially useful in the treatment of cell proliferation disorders, particularly cancer.

REFERENCES

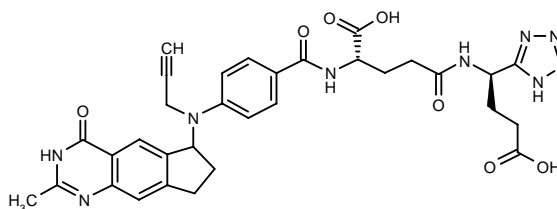
1. Wright, J.A. and Young, A.H. *Antitumor antisense sequences directed against ribonucleotide reductase*. US 5998383.

CB-300907*,1,3,4

233066

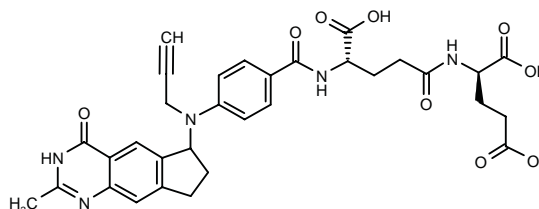
4(R)-[N-[4-[N-(2-Methyl-4-oxo-4,6,7,8-tetrahydro-3H-cyclopenta[g]quinazolin-6-yl)-N-(2-propynyl)amino]benzoyl]-L- γ -glutamylamino]-4-(1H-tetrazol-5-yl)butyric acid

N⁵-[3-Carboxy-1(R)-(1H-tetrazol-5-yl)propyl]-N²-[4-[N-(2-methyl-4-oxo-4,6,7,8-tetrahydro-3H-cyclopenta[g]quinazolin-6-yl)-N-(2-propynyl)amino]benzoyl]-L-glutamine



C32 H33 N9 O7; Mol wt: 655.6760

ACTION – Antineoplastic agent, an analogue of folic acid with thymidylate synthase-inhibitory activity ($K_i = 0.16$ nM) and the potential to be preferentially delivered to tumor cells via the α -isoform of the folate receptor (α -FR), as suggested by its high affinity for α -FR and low affinity for the reduced folate carrier ($K_m > 100$ μ M). Consistent with this proposed mechanism, compound showed high cytotoxic activity against human vulvar tumor A431 cells transfected with α -FR and cultured with physiological folate concentrations ($IC_{50} = 15$ nM) and in α -FR-expressing murine leukemia L1210 tumor cells cultured with low folate concentrations ($IC_{50} = 0.8$ nM), whereas it displayed much lower cytotoxicity in L1210 cells expressing the reduce folate carrier but not α -FR ($IC_{50} = 500$ nM). Another related compound is:



CB-300638 [282758]²⁻⁴: C32 H33 N5 O9

SOURCES – AstraZeneca; BTG.

REFERENCES

1. Bavetsias, V. et al. (BTG plc;Zeneca Ltd.) *Anti-cancer cpds. containing cyclopentaquinazoline ring*. EP 758328, GB 2290082, JP 1997512812, US 5747499, WO 9530673.

ACTION – Immunomodulating and antiinflammatory agent that acts by inhibiting IL-2 production in T-lymphocytes. It inhibited luciferase activity in an IL-2 promoter assay measuring transcriptional activation of a luciferase reporter gene with IC_{50} values below 10 μ M, and it is also reported to inhibit IL-2 production in stimulated human peripheral blood cells at similar concentrations. Furthermore, the compound inhibited the allogeneic cell transplant response in C57B1/6 mice to lymphocytes from the histoincompatible DBA strain by 74% at a dose of 100 mg/kg p.o. b.i.d. Particularly useful for preventing and treating immune disorders including organ transplant rejection, autoimmune diseases and inflammatory disorders.

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ONCOLYTIC DRUGS

ANTIMETABOLITES

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283749

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REFERENCES

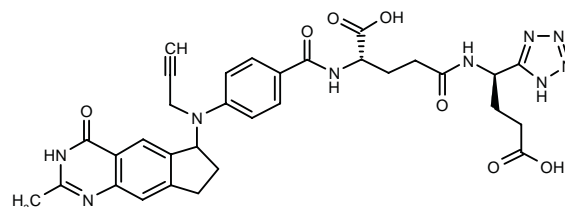
1. Wright, J.A. and Young, A.H. *Antitumor antisense sequences directed against ribonucleotide reductase*. US 5998383.

CB-300907*,1,3,4

233066

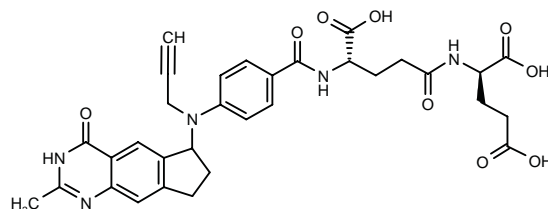
4(R)-[N-[4-[N-(2-Methyl-4-oxo-4,6,7,8-tetrahydro-3H-cyclopenta[g]quinazolin-6-yl)-N-(2-propynyl)amino]benzoyl]-L- γ -glutamylamino]-4-(1H-tetrazol-5-yl)butyric acid

N⁵-[3-Carboxy-1(R)-(1H-tetrazol-5-yl)propyl]-N²-[4-[N-(2-methyl-4-oxo-4,6,7,8-tetrahydro-3H-cyclopenta[g]quinazolin-6-yl)-N-(2-propynyl)amino]benzoyl]-L-glutamine



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SOURCES – AstraZeneca; BTG.

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2. Boyle, F. et al. (Zeneca Ltd.;BTG plc) *Tricyclic cpds. with pharmaceutical activity*. EP 667864, GB 2272217, JP 1996505838, US 5789417, WO 9411354.

3. Jackman, A. et al. *The potential role of the α -isoform of the folate receptor (α -FR) in the transport of two cyclopenta[g]quinazoline-based thymidylate synthase (TS) inhibitors with low affinity for the reduced-folate carrier (RFC)*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 565.

4. Theti, D. et al. *The human A431-FBP cell line transfected with the α -isoform of the folate receptor (α -FR) is highly sensitive to CB300907 and CB300638 in physiological folate concentrations*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 566.

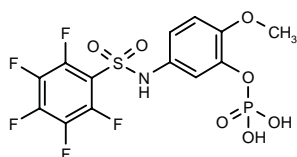
*Identified compound **233066** (see **231288**) Drug Data Rep 1996, 018(04): 0373.

ANTIMITOTIC DRUGS

282779³⁻⁵

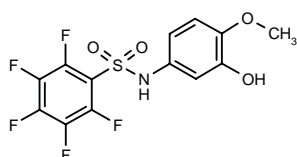
Phosphoric acid 2-methoxy-5-(2,3,4,5,6-pentafluorophenyl-sulfonamido)phenyl monoester

2,3,4,5,6-Pentafluoro-*N*-[4-methoxy-3-(phosphonooxy)-phenyl]benzenesulfonamide



C13 H9 F5 N O7 P S; Mol wt: 449.2441

ACTION – Antineoplastic agent, a phosphate prodrug of **282707**, an inhibitor of tubulin polymerization that covalently binds to β -tubulin and inhibits the growth and clonogenic potential of various tumor cell lines in culture. The prodrug, which combines good solubility, stability and the ability to generate the parent drug, was effective in inhibiting the growth of human mammary tumor MX-1 and cisplatin-resistant human ovarian tumor 2008/C13* xenografts in athymic nude mice.



282707¹⁻⁵: C13 H8 F5 N O4 S

SOURCE – Tularik.

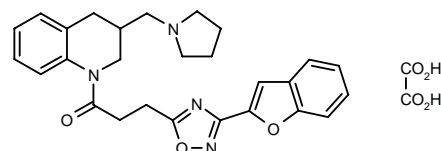
REFERENCES

- Clark, D. et al. (Tularik Inc.) *Pentafluorobenzenesulfonamides and analogs*. EP 896533, US 5880151, WO 9730677.
- Flygare, J. et al. (Tularik Inc.) *Pentafluorobenzenesulfonamides and analogs*. EP 939627, WO 9805315.
- Houze, J.B. (Tularik Inc.) *Arylsulfonamide phosphates*. WO 9967258.
- Houze, J. et al. *Cytotoxicity and antitumor activity of the phosphate prodrug of a novel microtubule inhibitor*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 635.
- Schwendner, S.W. et al. *A novel antitubulin agent and its phosphate prodrug effective against MX-1 human mammary tumor xenografts in athymic nude mice*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 636.

HORMONAL AGENTS

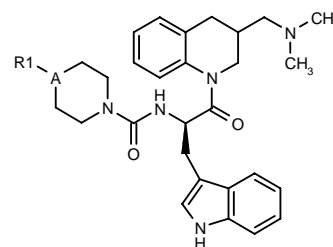
282130

3-[3-(Benzofuran-2-yl)-1,2,4-oxadiazol-5-yl]-1-[3-(1-pyrrolidinylmethyl)-1,2,3,4-tetrahydro-1-quinoliny]-1-propanone oxalate



C27 H28 N4 O3 . C2 H2 O4; Mol wt: 546.5770

ACTION – Somatostatin receptor agonist with high affinity for both human and rat sst4 receptors ($IC_{50} = 7$ and 10 nM, respectively); agonist activity was demonstrated by its ability to inhibit forskolin-stimulated cAMP accumulation in rat astrocytes (43% inhibition at 10 nM). Potentially useful for the treatment of intracellular signal transduction disorders, proliferative diseases or hormone-dependent disorders. Within this series of amine derivatives, the following are also included:



Compound	R1	A	Formula
282131	Ph	N	C ₃₄ H ₄₀ N ₆ O ₂
282132	2-oxo-2,3-dihydro-1-benzimidazolyl	CH	C ₃₆ H ₄₁ N ₇ O ₃

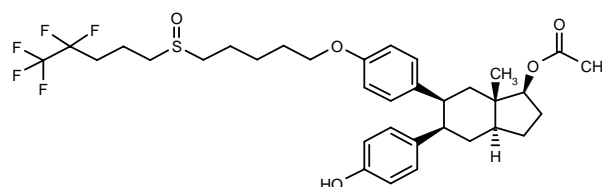
SOURCE – Takeda.

REFERENCES

- Suzuki, N. et al. (Takeda Chemical Industries, Ltd.) *Amine cpds., their production and their use as somatostatin receptor antagonists or agonists*. WO 9952875.

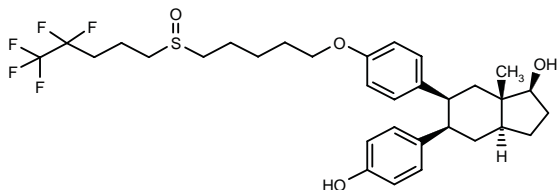
284451

(1*S*,3*aS*,5*R*,6*S*,7*aS*)-1-Acetoxy-5-(4-hydroxyphenyl)-7a-methyl-6-[4-[5-(4,4,5,5,5-pentafluoropentylsulfanyl)-pentyloxy]phenyl]perhydroindene



C34 H43 F5 O5 S; Mol wt: 658.7647

ACTION – Antiestrogenic agent for the treatment of estrogen-dependent disorders such as breast or endometrial cancer, prostatic hyperplasia, prostatic carcinoma, anovular infertility and melanoma, as well as for use in hormone replacement therapy. *In vivo*, compound exhibited potent antiuterotrophic effects in immature rats (55% inhibition at 0.3 mg s.c.). Another compound from this series of 3,4-diphenylbicyclo[4.3.0]nonyl derivatives is:



284452: C32 H41 F5 O4 S

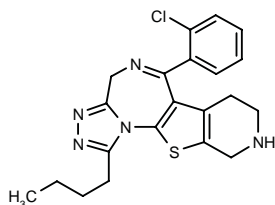
SOURCE – Schering AG.

REFERENCES

1. Klar, U. et al. (Schering AG) *Novel antiestrogens, a method for the production thereof, and their pharmaceutical application*. DE 19826213, WO 9964393.

284584

1-Butyl-6-(2-chlorophenyl)-7,8,9,10-tetrahydro-4H-pyrido[4',3':4,5]thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine



C21 H22 Cl N5 S; Mol wt: 411.9588

ACTION – Somatostatin receptor modulator with potential in the treatment of disorders where somatostatin receptors are involved, particularly acromegaly, hypophysial adenoma or endocrine gastroenteropancreatic tumors.

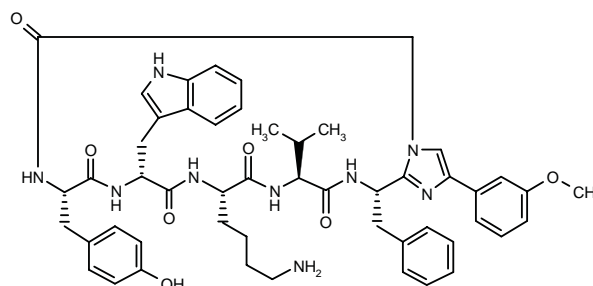
SOURCE – SCRAS.

REFERENCES

1. Bigg, D. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Use of diazepines for preparing medicines for treating pathological conditions or diseases involving one of the growth hormone release inhibiting factor receptors*. FR 2779652, WO 9965917.

284586

Cyclo[L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-phenylalanyl-ψ[4-(3-methoxyphenyl)imidazole-2,1-diyl]]glycyl]



C51 H59 N9 O7; Mol wt: 910.0831

ACTION – A representative compound from a series of cyclic somatostatin analogues with potential in the treatment of a broad range of disorders involving somatostatin receptors such as prolactin-secreting adenomas, restenosis, diabetes mellitus, insulin insensitivity, gastric acid secretion, peptic ulcers, irritable bowel syndrome, cancer, angiogenesis, inflammatory disorders and angioplasty.

SOURCE – SCRAS.

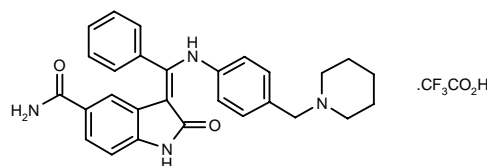
REFERENCES

1. Gordon, T.D. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Cyclic somatostatin analogs*. WO 9965942.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

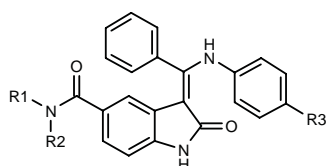
282207

2-Oxo-3-[(Z)-1-phenyl-1-[4-(1-piperidinylmethyl)phenylamino]methylene]-2,3-dihydro-1H-indole-5-carboxamide trifluoroacetate



C28 H28 N4 O2 . C2 H F3 O2; Mol wt: 566.5771

ACTION – Antiproliferative agent shown to inhibit cyclin-dependent kinases and cyclin/CDK complexes and the proliferation of human leiomyosarcoma SK-UT-1B cells (IC_{50} = 0.01 μ M). Other specifically claimed substituted indolinones are:



Compound	R1=R2	R3	Formula
282208	H	CH ₂ NH ₂	C ₂₃ H ₂₀ N ₄ O ₂
282209	H	H	C ₂₂ H ₁₇ N ₃ O ₂
282210	H	Br	C ₂₂ H ₁₆ BrN ₃ O ₂
282211	H	CH ₂ N(Me) ₂	C ₂₅ H ₂₄ N ₄ O ₂
282212	H	1-pyrrolidinyl-CH ₂	C ₂₇ H ₂₆ N ₄ O ₂
282213	H	hexahydro-1H-azepin-1-yl-CH ₂	C ₂₉ H ₃₀ N ₄ O ₂
282214	H	4-(PhCH ₂)-1-Pip-CH ₂	C ₃₅ H ₃₄ N ₄ O ₂
282215	H	CH ₂ NHBu	C ₂₇ H ₂₈ N ₄ O ₂
282217	H	CH ₂ N(Me)CH ₂ Ph	C ₃₁ H ₂₈ N ₄ O ₂
282218	Me	1-Pip-CH ₂	C ₃₀ H ₃₂ N ₄ O ₂
282219	Et	1-Pip-CH ₂	C ₃₂ H ₃₆ N ₄ O ₂
282220	H	CH ₂ NHCH ₂ Ph	C ₃₀ H ₂₈ N ₄ O ₂
282221	H	O(CH ₂) ₃ N(Me) ₂	C ₂₇ H ₂₈ N ₄ O ₃

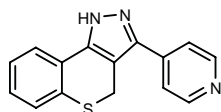
SOURCE – Boehringer Ingelheim.

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282641

3-(4-Pyridyl)-1,4-dihydro[1]benzothiopyrano[4,3-*c*]pyrazole



C₁₅H₁₁N₃S; Mol wt: 265.3389

ACTION – An inhibitor of tyrosine kinases involved in angiogenic and/or edematous processes such as KDR tyrosine kinase (IC₅₀ = 13.4 μM). Claimed for the treatment of cancer, arthritis, atherosclerosis, psoriasis, hemangioma, myocardial angiogenesis, ischemic limb angiogenesis, corneal disease, neovascular glaucoma, macular degeneration, wound healing, *Helicobacter pylori*-related diseases, fractures, diabetic retinopathy, burns, chronic lung disease, stroke, polyps, psoriasis, allergic inflammation, ovarian hyperstimulation syndrome and brain tumor-associated cerebral edema.

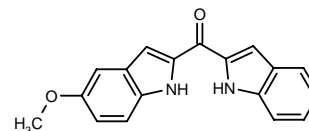
SOURCE – BASF.

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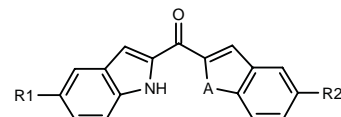
282820

1-(1*H*-Indol-2-yl)-1-(5-methoxy-1*H*-indol-2-yl)methanone



C₁₈H₁₄N₂O₂; Mol wt: 290.3206

ACTION – Agent for the treatment of cancer, arteriosclerosis, restenosis, arthritis and fibrotic disorders, an inhibitor of platelet-derived growth factor (PDGF) receptor tyrosine kinase proven to inhibit PDGF receptor phosphorylation *in vitro* in Swiss 3T3 cells and isolated Swiss 3T3-derived membranes with IC₅₀ values of 0.1-0.3 and < 0.03 μM, respectively, while exhibiting no effect against epidermal growth factor (EGF) receptor tyrosine kinase or src kinase phosphorylation in A431 and src-NIH cells, respectively (IC₅₀ > 10 and > 30 μM, respectively). Other specifically claimed compounds from this series of indole derivatives include the following:



Compound	R1	R2	A	Formula
282821	OMe	OMe	NH	C ₁₉ H ₁₆ N ₂ O ₃
282822	OMe	H	S	C ₁₈ H ₁₃ NO ₂ S
282823	OH	H	NH	C ₁₇ H ₁₂ N ₂ O ₂
282824	H	H	NH	C ₁₇ H ₁₂ N ₂ O
282825	4-morpholinyl-CH ₂ CH ₂ O	H	NH	C ₂₃ H ₂₃ N ₃ O ₃
282826	OCH ₂ CH ₂ N(Me) ₂	H	NH	C ₂₁ H ₂₁ N ₃ O ₂
282828	Oac	H	NH	C ₁₉ H ₁₄ N ₂ O ₃
282829	OCOPr	H	NH	C ₂₁ H ₁₈ N ₂ O ₃
282830	OCOCH ₂ N(Me) ₂	H	NH	C ₂₁ H ₁₉ N ₃ O ₂
282831	OCOEt	H	NH	C ₂₀ H ₁₆ N ₂ O ₃
282832	2-thienyl-CH ₂ COO	H	NH	C ₂₅ H ₁₈ N ₂ O ₃ S

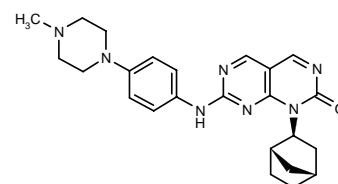
SOURCE – Asta Medica.

REFERENCES

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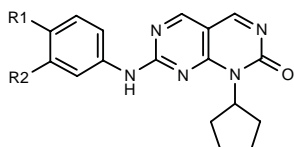
283750

1-(*exo*-Bicyclo[2.2.1]hept-2-yl)-7-[4-(4-methylpiperazin-1-yl)phenylamino]pyrimido[4,5-*d*]pyrimidin-2(1*H*)-one

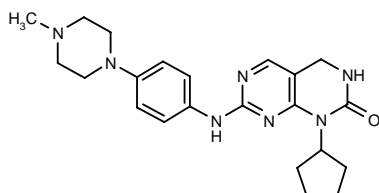


C₂₄H₂₉N₇O; Mol wt: 431.5411

ACTION – Potent inhibitor of cyclin-dependent kinases and tyrosine kinases, especially active against cdc2, cdk2 and cdk4, as well as platelet-derived growth factor (PDGF) receptor, fibroblast growth factor (FGF) receptor and c-Src tyrosine kinases. Potentially useful in the treatment of cell proliferative disorders such as cancer, atherosclerosis, restenosis, angiogenesis, diabetic retinopathy, psoriasis and endometriosis. Other exemplified bicyclic pyrimidines and bicyclic 3,4-dihydropyrimidines include the following:



Compound	R1	R2	Formula
283752	4-Me-1-Piz	H	C ₂₂ H ₂₇ N ₇ O
283753	4-OH-1-Pip	H	C ₂₂ H ₂₆ N ₆ O ₂
283754	OCH ₂ CH ₂ N(Et) ₂	Me	C ₂₄ H ₃₂ N ₆ O ₂
283755	3-OH-1-Pip	H	C ₂₂ H ₂₆ N ₆ O ₂



283751: C₂₂ H₂₉ N₇ O

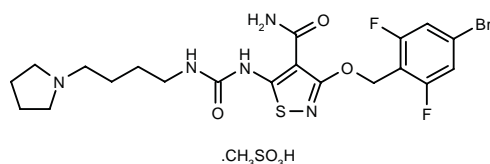
SOURCE – Warner-Lambert.

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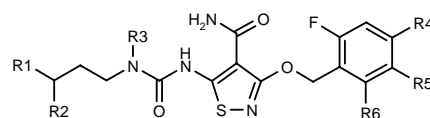
283989

3-(4-Bromo-2,6-difluorobenzyloxy)-5-[3-[4-(1-pyrrolidinyl)butyl]ureido]isothiazole-4-carboxamide mesylate



C₂₀ H₂₄ Br F₂ N₅ O₃ S . C H₄ O₃ S; Mol wt: 628.5132

ACTION – Antiproliferative agent that acts by inhibiting KDR/FLK-1 (vascular endothelial growth factor [VEGF]) receptor kinase associated with the proliferation of endothelial cells and, more particularly, vasculogenesis and angiogenesis. As such, it is expected to be useful for the treatment of hyperproliferative disorders such as cancer and benign prostatic hyperplasia. Other specifically claimed isothiazole derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
283990	H	4-Me-1-Piz	H	Me	H	H	C ₂₁ H ₂₉ FN ₆ O ₃ S
283991	H	1-Pip-CH ₂	H	Cl	H	F	C ₂₁ H ₂₆ ClF ₂ N ₅ O ₃ S
283992	H	2-(HOCH ₂)-1-pyrrolidinyl-CH ₂	H	Cl	H	F	C ₂₁ H ₂₆ ClF ₂ N ₅ O ₄ S
283993	H	4-Me-1-Piz	H	Br	F	F	C ₂₀ H ₂₄ BrF ₃ N ₆ O ₃ S
283994	H	i-PrNH	H	Me	F	F	C ₁₉ H ₂₄ F ₃ N ₅ O ₃ S
283995	OH	1-pyrrolidinyl-CH ₂ CH ₂	H	Cl	F	F	C ₂₁ H ₂₅ ClF ₃ N ₅ O ₄ S
283996	H	NH ₂	Me	Me	F	F	C ₁₇ H ₂₀ F ₃ N ₅ O ₃ S

SOURCE – Pfizer.

REFERENCES

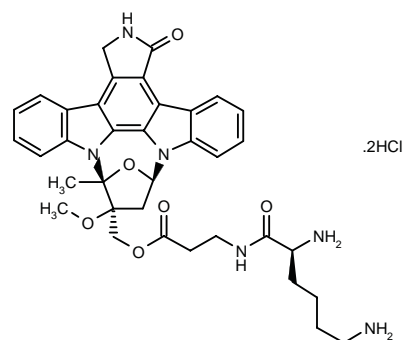
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CEP-2563^{1,5,7,10,13,19,22,23,25-27,29-34}

238846

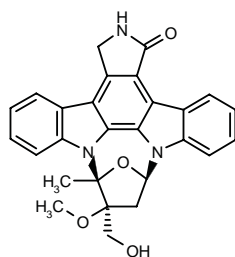
L-Lysyl-β-alanine 9(S),12(R)-epoxy-10(S)-methoxy-9-methyl-1-oxo-2,3,9,10,11,12-hexahydro-1H-diindolo-[1,2,3-fg:3',2',1'-k']pyrrolo[3,4-η][1,6]benzodiazocin-10-ylmethyl ester dihydrochloride

KT-8391



C₃₆ H₄₀ N₆ O₆ . 2HCl; Mol wt: 725.6698

ACTION – Antineoplastic agent, a potent and orally active inhibitor of growth factor receptor-linked tyrosine kinase, a prodrug ester of **CEP-751**; it is slowly metabolized *in vivo* to CEP-751, the predominant form in plasma, and CEP-701⁺, another active metabolite. Compound showed improved aqueous solubility (> 200 mg/ml) versus the parent compound and was active against both androgen-sensitive and -insensitive prostate cancer in rats (Dunning H and AT-2 tumors, respectively), inducing significant regression of tumor size 14 days after treatment with 16 mg/kg/day p.o. or s.c. A phase I clinical study in patients with advanced incurable solid tumors demonstrated that compound infused i.v. for 1 h 3 days per week for 3 weeks is well tolerated up to the dose of 64 mg/m², with no hematological toxicity.



**CEP-751 [252141]^{1-4,6,8-28}
(KT-6587)**

SOURCES – Cephalon; Kyowa Hakko; Schwarz; TAP.

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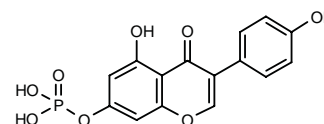
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*Drug Data Rep 1999, 021(11): 1025.

GENISTEIN-7-PHOSPHATE

284427

Phosphoric acid 5-hydroxy-3-(4-hydroxyphenyl)-4-oxo-4H-1-benzopyran-7-yl monoester



C15 H11 O8 P; Mol wt: 350.2179

ACTION – Prodrug of the known isoflavone genistein with increased aqueous solubility and bioavailability compared to parent compound. Potentially useful for the treatment of cancer, osteoporosis and estrogen-related diseases, to protect skin from UV radiation damage, as well as for use as an antioxidant, immunostimulant or as a nutritional supplement.

SOURCE – Vyrex.

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ISIS-14864

284607

15-Mer chimeric phosphorothioate oligonucleotide whose sequence is: 5'-AGCGCGCGATGAATT-3', in which the first eight nucleotides at the 5'-end are 2'-deoxynucleotides and the remaining seven nucleotides are 2'-O-methoxyethyl-substituted

ACTION – Reduced-length antisense oligonucleotide targeted to nucleic acids encoding protein kinase C (PKC), found to inhibit PKC- α mRNA in human lung carcinoma A549 cells by 79% at 200 nM. Its activity was better than that of the 20-mer phosphorothioate oligodeoxynucleotide ISIS-3521 in this assay, with respective IC₅₀ values of 50 nM and 100 nM. *In vivo* in nude mice bearing human glioblastoma U-87 xenografts, ISIS-14864 reduced tumor volume by 96% at a dose of 2 mg/kg/day i.p. for 28 days (vs. 39% for ISIS-3521), and it improved survival (5 of 7 animals alive at day 28 vs. 0 of 8 on ISIS-3521) and significantly reduced tumor growth rate (82% vs. 29% on ISIS-3521).

SOURCE – Isis Pharmaceuticals.

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ISIS-28313

285044

18-Mer chimeric phosphorothioate oligonucleotide whose sequence is: 5'-GCCCTGGTTGACCGACTG-3', in which the central ten nucleotides are 2'-deoxynucleotides, the last four nucleotides flanking 5'- and 3'-ends are 2'-O-methoxyethylnucleotides and the cytidine residues in these two regions are 5-methylcytidines

ACTION – Antisense oligonucleotide useful for modulating the expression of human SMAD3, a member of the subgroup of SMAD family transcription factors which is an integral component of the TGF- β signaling cascade; elevated SMAD3 expression is thought to be associated with neoplasia. ISIS-28313 was proven to inhibit SMAD3 mRNA levels by 90% at 150 nM in human cells.

SOURCE – Isis Pharmaceuticals.

REFERENCES

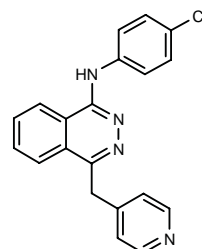
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PTK-787*

271217

N-(4-Chlorophenyl)-4-(pyridin-4-ylmethyl)phthalazin-1-amine

CGP-79787
ZK-222584



C20 H15 Cl N4; Mol wt: 346.8195

ACTION – Orally active antineoplastic agent with inhibitory activity against vascular endothelial growth factor (VEGF) receptor tyrosine kinase (IC₅₀ = 0.1-0.26 μ M) and high selectivity over kinases from other receptor families including epidermal growth factor (EGF), fibroblast growth factor (FGF-1, FGF-2), Tek, c-Src, v-Abl and protein kinase C (PKC). In the submicromolar range, compound also inhibited KDR and platelet-derived growth factor (PDGF) receptor autophosphorylation, the proliferation of human umbilical vein endothelial cells (HUVEC) and the sprouting of rat aortic pieces cultured in a fibrin gel. Compound did not have any cytotoxic or antiproliferative activity against cells not expressing VEGF receptors. At doses of 12.5-50 mg/kg/day p.o., it dose-dependently inhibited VEGF- and PDGF-induced angiogenesis in an *in vivo* mouse growth factor implant model and inhibited tumor growth in nude mice bearing s.c.-implanted human epidermoid carcinoma A-431 tumors or VEGF-dependent human ovarian carcinoma SKOV3. Preliminary data from a phase I clinical study in advanced cancer patients demonstrated that compound is well tolerated, is rapidly absorbed with a t_{max} of 1.1-2.0 h, has a terminal half-life of 4.5 h and is not associated with accumulation following once-daily dosing.

SOURCES – Novartis; Schering AG.

REFERENCES

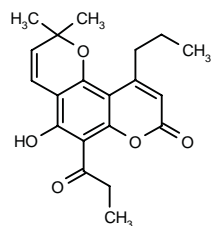
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*Identified compound **271217** Drug Data Rep 1999, 021(02): 0175.

WHI-D12

282716

5-Hydroxy-2,2-dimethyl-6-propionyl-10-propyl-2,8-dihydropyrano[2,3-f]-1-benzopyran-8-one



C20 H22 O5; Mol wt: 342.3888

ACTION – Antineoplastic agent, a selective Bruton's tyrosine kinase inhibitor (BTK; IC_{50} ~29 μ M) that is inactive against Janus kinases JAK1, JAK2 or JAK3, Src kinase HCK, Zap/Syk kinase SYK or insulin receptor kinase (IRK). Molecular modeling showed that compound can interact with specific amino acid residues in the catalytic site of BTK, contributing to its enhanced binding affinity. It is reported to be able to promote apoptotic cell death in human leukemia cells and may be a lead for the development of novel anticancer agents.

SOURCE – Hughes Institute, Roseville, MN (US).

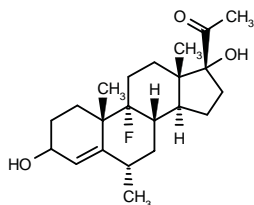
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ANGIOGENESIS INHIBITORS

282100

9 α -Fluoro-3,17 α -dihydroxy-6 α -methylpregn-4-en-20-one



C22 H33 F O3; Mol wt: 364.4977

ACTION – Agent for the treatment of cancer, diabetic retinopathy and rheumatism that acts by inhibiting angiogenesis, as demonstrated in rabbits with DMBA-induced mammary tumors implanted into the cornea, where compound was found to significantly inhibit neovascularization at a dose of 0.3 mg/pellet.

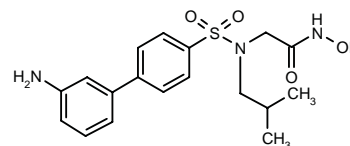
SOURCE – Meiji Milk Products.

REFERENCES

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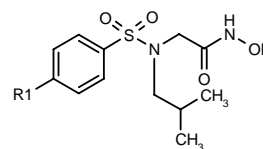
282125

2-[N-(3'-Aminobiphenyl-4-ylsulfonyl)-N-isobutylamino]-acetohydroxamic acid



C18 H23 N3 O4 S; Mol wt: 377.4627

ACTION – An inhibitor of matrix metalloproteinases (MMPs), particularly gelatinase A (MMP-2; IC_{50} = 2.7 nM) and gelatinase B (MMP-9; IC_{50} = 0.73 nM), with selectivity relative to fibroblast collagenase (MMP-1; IC_{50} = 3.3 μ M) and MMP-14 (IC_{50} = 0.24 μ M). Potentially useful for the treatment of tumor growth and metastasis. Other compounds from this series of sulfonamide derivatives include the following:



Compound	R1	Formula
282126	4-Me-PhCONH	C ₂₀ H ₂₅ N ₃ O ₅ S
282127	5-Me-2-thienyl-CONH	C ₁₈ H ₂₃ N ₃ O ₅ S ₂
282128	4-Me-Ph	C ₁₉ H ₂₄ N ₂ O ₄ S
282129	4-MeO-Ph	C ₁₉ H ₂₄ N ₂ O ₅ S

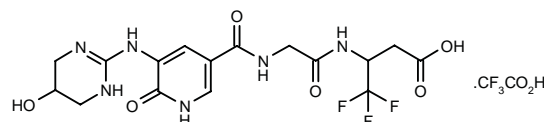
SOURCE – Kotobuki.

REFERENCES

1. Tomiyama, T. et al. (Kotobuki Pharmaceutical Co., Ltd.) *Sulfonamide derivs., their preparation method, and medicinal compsns. containing them*. JP 1999236369.

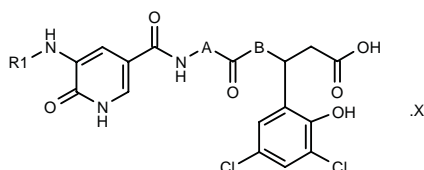
282264

4,4,4-Trifluoro-3-[2-[5-(5-hydroxy-1,4,5,6-tetrahydropyrimidin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-ylcarboxamido]acetamido]butyric acid trifluoroacetate

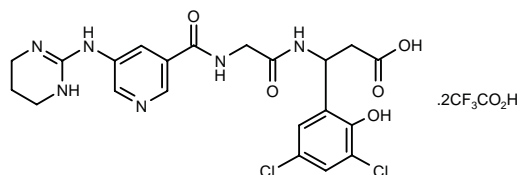


C16 H19 F3 N6 O6 . C2 H F3 O2; Mol wt: 562.3780

ACTION – Vitronectin ($\alpha_v\beta_3$ integrin) antagonist that exhibits high affinity for the human $\alpha_v\beta_3$ receptor and selectivity relative to the human gpIIb/IIIa receptor, giving respective IC_{50} values of 1.5 and 20,630 nM in binding assays. Potentially useful for treating tumor metastasis, solid tumor growth and angiogenesis, osteoporosis, hypercalcemia of malignancy, smooth muscle cell migration, restenosis, rheumatoid arthritis and macular degeneration. Other exemplified heterocyclic glycyll β -alanine derivatives include the following:



Compound	R1	A	B	Isomer	X	Formula
282266	4,5-dihydro-2-imidazolyl	CH2	NH		CF3CO2H	C ₂₀ H ₂₀ Cl ₂ N ₆ O ₈ .C ₂ HF ₃ O ₂
282267	5,5-(Me)2-1,4,5,6-tetrahydro-2-pyrimidinyl	NH	CH2	S	CF3CO2H .H2O	C ₂₃ H ₂₆ Cl ₂ N ₆ O ₈ .C ₂ HF ₃ O ₂ .H ₂ O
282268	4,5-dihydro-2-imidazolyl	CH2	NH	R	CF3CO2H .H2O	C ₂₀ H ₂₀ Cl ₂ N ₆ O ₈ .C ₂ HF ₃ O ₂ .H ₂ O



282265: C₂₁ H₂₂ Cl₂ N₆ O₅ . 2 C₂ H F₃ O₂

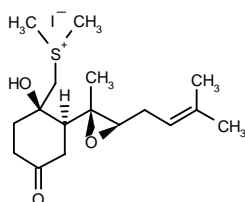
SOURCE – Searle (Pharmacia).

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1. Chandrakumar, N.S. et al. (G.D. Searle & Co.) *Heterocyclic glycyll β -alanine derivs. as vitronectin antagonists*. WO 9952896.

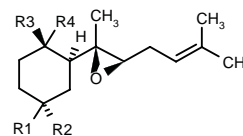
283549

[1(*R*)-Hydroxy-2(*S*)-[2(*R*)-methyl-3(*R*)-(3-methyl-2-buten-yl)oxiran-2-yl]-4-oxocyclohexylmethyl]dimethylsulfonium iodide



C₁₇ H₂₉ I O₃ S; Mol wt: 440.3791

ACTION – Angiogenesis inhibitor, a fumagillol derivative shown to inhibit the proliferation of calf pulmonary artery endothelial (CPAE) cells and murine lymphoma EL-4 cells (IC_{50} = 12 and 32 μ g/ml, respectively, vs. 3.2 and 1.6 mg/ml for fumagillin), while being ineffective against murine leukemia P388D1 cells (IC_{50} = 10 g/ml or more). LD_{50} = 2.5 g/kg p.o. or more in mice. Potentially useful in the treatment of cancer, rheumatoid arthritis, psoriasis or diabetic retinitis. Other compounds from this series of 5-demethoxyfumagillol derivatives include the following:



Compound	R1	R2	R3	R4	Formula
283551		-O-	OH	CH ₂ Cl	C ₁₅ H ₂₃ ClO ₃
283552	H	OCONHCOCH ₂ Cl	-OCH ₂ -		C ₁₈ H ₂₆ ClNO ₅
283555	H	3,4,5-(MeO)3-PhCH=CHCOO	-OCH ₂ -		C ₂₇ H ₃₆ O ₇
283557	H	4-Cl-PhCH=CHCOO	-OCH ₂ -		C ₂₄ H ₂₉ ClO ₄
283559	H	4-MeO-PhCH ₂ CH ₂ COO	-OCH ₂ -		C ₂₈ H ₃₄ O ₅
283560	H	OCO ₂ CH ₂ Ph	-OCH ₂ -		C ₂₃ H ₃₀ O ₅
283561	H	4-N(Me)2-PhCH=CHCONH	-OCH ₂ -		C ₂₆ H ₃₆ N ₂ O ₃

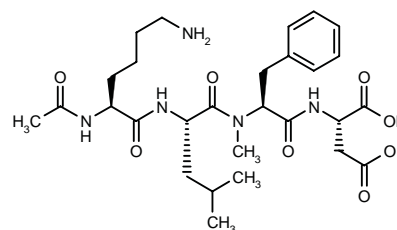
SOURCE – Chong Kun Dang.

REFERENCES

1. Hong, C.I. et al. (Chong Kun Dang Corp.) *5-Demethoxyfumagillol derivs. and processes for preparing the same*. WO 9959987.

283746

N-Acetyl-L-lysyl-L-leucyl-*N*-methyl-L-phenylalanyl-L-aspartic acid



C₂₈ H₄₃ N₅ O₈; Mol wt: 577.6747

ACTION – Antiangiogenic agent producing 83% inhibition of human microvascular endothelial cell migration at a concentration of 10 nM. Potentially useful in the treatment of cancer, arthritis and retinopathy.

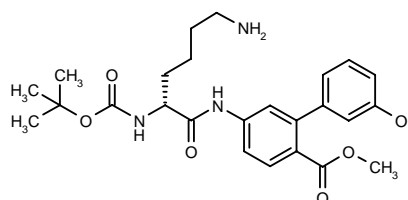
SOURCE – Abbott.

REFERENCES

1. Kawai, M. et al. (Abbott Laboratories Inc.) *Antiangiogenic drug to treat cancer, arthritis and retinopathy*. WO 9961466.

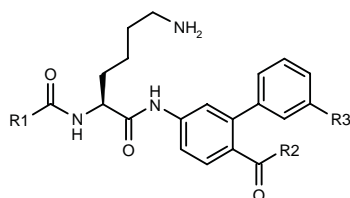
283819

5-[*N*-(*tert*-Butoxycarbonyl)-D-lysylamino]-3'-hydroxy-biphenyl-2-carboxylic acid methyl ester



C₂₅ H₃₃ N₃ O₆; Mol wt: 471.5507

ACTION – Antiangiogenic compound that inhibits human microvascular endothelial cell migration (> 95% inhibition at 200 nM). Potentially useful for the treatment of cancer, arthritis and retinopathy. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
283822	Me	-L-Asn-OH	H	C ₂₅ H ₃₁ N ₅ O ₆
283824	t-BuO	OH	OH	C ₂₄ H ₃₁ N ₃ O ₆

SOURCE – Abbott.

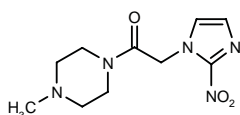
REFERENCES

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TX-1920

282720

1-(4-Methylpiperazin-1-yl)-2-(2-nitro-1H-imidazol-1-yl)-1-ethanone



C₁₀ H₁₅ N₅ O₃; Mol wt: 253.2605

ACTION – Antineoplastic agent, an antiangiogenic and hypoxic radio- and chemosensitizing agent proven to inhibit rat lung endothelial cell proliferation *in vitro* (IC₅₀ = 90 μM); its antiangiogenic activity was similar to that of TX-1877 in the chorioallantoic membrane assay (CAM). Its radiosensitizing activity was demonstrated in EMT6/KU cells under hypoxic conditions.

SOURCES – Tokushima Bunri University, Tokushima, (JP); Tokyo Metropolitan Institute of Medical Science, Tokyo (JP).

REFERENCES

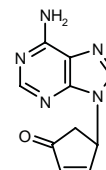
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2. Yamashita, M. et al. *Molecular design of anti-angiogenic hypoxic cell radio and chemosensitizer*. Jpn J Cancer Res 1999, 90(Suppl.): Abst 2450.

OTHER ONCOLYTIC DRUGS

281999

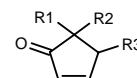
4-(6-Amino-9H-purin-9-yl)cyclopent-2-en-1-one

4-(Adenin-9-yl)cyclopent-2-en-1-one

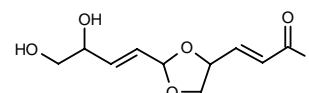


C₁₀ H₉ N₅ O; Mol wt: 215.2151

ACTION – Antineoplastic and apoptosis-inducing agent shown to inhibit the viability of human leukemia HL-60 cells with an IC₅₀ value of 22.4 μM. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
282000	H	H	guanin-9-yl	C ₁₀ H ₉ N ₅ O ₂
282001	OH		-O-	C ₉ H ₈ O ₃



282002: C₁₀ H₁₄ O₅

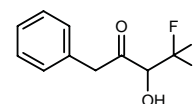
SOURCE – Takara Shuzo.

REFERENCES

1. Tatsumi, Y. et al. (Takara Shuzo Co., Ltd.) *Substances capable of inducing apoptosis*. WO 9936383.

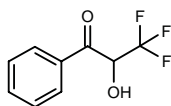
282754¹⁻⁴

4,4,4-Trifluoro-3-hydroxy-1-phenylbutan-2-one



C₁₀ H₉ F₃ O₂; Mol wt: 218.1731

ACTION – Lead antineoplastic agent with selective *in vitro* cytotoxicity against the human oral tumor cell lines human squamous cell carcinoma HSC-2 and salivary gland tumor HSG (CC₅₀ = 22 and 110 μM, respectively) as compared with human gingival fibroblasts (HGF; CC₅₀ = 310 μM). Compound was able to induce apoptosis in HSG cells, and this effect appeared to be mediated by a caspase pathway. Another trifluoromethyl ketone is:



2827532-4: C₉ H₇ F₃ O₂

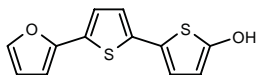
SOURCES – Josai University, Sakado (JP); Meiji Pharmaceutical University, Tokyo (JP); Meikai University, Urayasu (JP).

REFERENCES

1. Kamitori, Y. et al. *Convenient synthesis of 1,1,1-trifluoro-4,5-diaza-2,4-alkadienes and 1-aryl-3,3,3-trifluoro-1-propanones*. *Synthesis* 1989, (1): 43.
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3. Kawase, M. and Kurihara, T. *A convenient synthesis of alpha-trifluoromethylated and alpha-perfluoroalkylated acylolins from alpha-hydroxy acids*. *Tetrahedron Lett* 1994, 35(44): 8209.
4. Kawase, M. et al. *α-Trifluoromethylated acylolins induce apoptosis in human oral tumor cell lines*. *Bioorg Med Chem Lett* 1999, 9(21): 3113.

283485

5-[5-(2-Furyl)thien-2-yl]thiophen-2-ol



C₁₂ H₈ O₂ S₂; Mol wt: 248.3252

ACTION – Antineoplastic agent, a representative polyheterocyclic compound proven active in the NCI screening assay, where it gave GI₅₀ values of < 100 μM for all cell lines tested and < 10 nM for 12 cell lines.

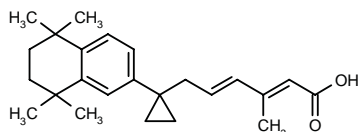
SOURCE – Industrial Technology & Research Institute, Hsinchu (TW).

REFERENCES

1. Chang, C.T. and Yang, Y.-L. (Industrial Technology & Research Institute) *Polyheterocyclic cpds*. US 5994394.

283934

3-Methyl-6-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]hexa-2(E),4(E)-dienoic acid



C₂₄ H₃₂ O₂; Mol wt: 352.5148

ACTION – Dienoic retinoid with panagonist activity at retinoic acid receptor (RAR) and retinoid X receptor (RXR) subtypes, as demonstrated in a cotransfection assay in CV-1 cells (EC₅₀ = 59, 17, 24, 13, 6 and 14 nM for RARα, RARβ, RARγ, RXRα, RXRβ and RXRγ subtypes, respectively, vs. EC₅₀ = 220, 29, 50, 195, 128 and 124 nM, respectively, for 9-*cis*-retinoic acid), as well as in a binding assay (K_d = 644, 463, 552, 2, 6 and 8 nM, respectively). In addition, it was shown to inhibit the growth of human myeloma RPMI 8226, human cervical epidermoid carcinoma ME-180 and human acute monocytic leukemia AML-193 cells with respective IC₅₀ values of < 0.1, 0.9 and < 0.1 nM, being more potent than 9-*cis*-retinoic acid (IC₅₀ = 150, 180 and 113 nM, respectively). Potentially useful for the treatment of skin-related diseases, cancer, ocular diseases, cardiovascular, inflammatory, neurodegenerative or immune diseases, diseases involving human papilloma-virus, wound healing or restoration of hair growth.

SOURCE – Ligand.

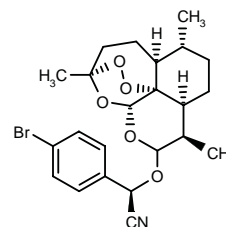
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284484

2(*R*)-(4-Bromophenyl)-2-[(3*R*,5*aS*,6*R*,8*aS*,9*R*,12*R*,12*aR*)-3,6,9-trimethylperhydro-3,12-epoxypyrano[4,3-*j*]-1,2-benzodioxepin-10-yl]acetoneitrile

10-[1(*R*)-(4-Bromophenyl)-1-cyanomethoxy]-10-deoxyartemisinin



C₂₃ H₂₈ Br N O₅; Mol wt: 478.3802

ACTION – Antineoplastic and apoptosis-inducing agent, a representative compound from a series of artemisinin derivatives.

SOURCES – ADIR; Shanghai Institute of Materia Medica, Shanghai (CN).

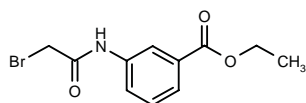
REFERENCES

1. Li, Y. et al. (Shanghai Institute of Materia Medica; ADIR et Cie.) *Artemisinin derivs., method for the preparation thereof and pharmaceutical compsns. containing the same*. WO 9965914.

3-BAABE

282727

3-(2-Bromoacetamido)benzoic acid ethyl ester



C11 H12 Br N O3; Mol wt: 286.1238

ACTION – Antineoplastic agent with strong *in vitro* cytotoxic activity against human leukemia and lymphoma cells ($IC_{50} < 0.2 \mu\text{g/ml}$), as well as prostate, colon, ductal and kidney cancer cell lines ($IC_{50} = 0.8\text{--}0.88 \mu\text{g/ml}$). The susceptibility of human lymphoma cells to compound did not appear to be affected by multidrug resistance (MDR) phenotypes, and its cytotoxic activity did not depend on changes in the cell cycle, but appeared to be mediated by an apoptotic mechanism involving a pathway that is specifically limited to activation of caspase 9.

SOURCE – Mount Sinai School of Medicine, New York, NY (US).

REFERENCES

- Schlesinger, M. et al. 3-Bromoacetyl amino benzoic acid ethyl ester (3-BAABE): A cancericidal agent which acts as an activator of apoptosis effector caspase-9. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 281.

CARIN

Human carboxypeptidase inhibitor polypeptide

284522

ACTION – Human carboxypeptidase inhibitor (CARIN), a polypeptide whose expression is associated with cell proliferation, cancer, inflammation, immune response and fetal/infant development. Polynucleotides encoding this polypeptide, as well as expression vectors, agonists, antibodies and antagonists, are also provided.

SOURCE – Incyte.

REFERENCES

- Hillman, J.L. and Lal, P. (Incyte Pharmaceuticals, Inc.) New human carboxypeptidase inhibitor. WO 9964609.

PSP-94

272445

H-Ser-Cys-Tyr-Phe-Ile-Pro-Asn-Glu-Gly-Val-Pro-Gly-Asp-Ser-Thr-Arg-Lys-Cys-Met-Asp-Leu-Lys-Gly-Asn-Lys-His-Pro-Ile-Asn-Ser-Glu-Trp-Gln-Thr-Asp-Asn-Cys-Glu-Thr-Cys-Thr-Cys-Tyr-Glu-Thr-Glu-Ile-Ser-Cys-Cys-Thr-Leu-Val-Ser-Thr-Pro-Val-Gly-Tyr-Asp-Lys-Asp-Asn-Cys-Gln-Arg-Ile-Phe-Lys-Lys-Glu-Asp-Cys-Lys-Tyr-Ile-Val-Val-Glu-Lys-Lys-Asp-Pro-Lys-Lys-Thr-Cys-Ser-Val-Ser-Glu-Trp-Ile-Ile-OH

β -Inhibin

ACTION – Antineoplastic agent, a cysteine-rich 94-amino-acid protein synthesized primarily in the prostate gland, with proapoptotic properties and shown in preclinical models to inhibit the growth of hormone-refractory prostate cancer. Compound was able to inhibit both the growth and the clonogenicity of prostate cancer PC-3 cells in a concentration-dependent manner (0.01-20 and 0.001-1 $\mu\text{g/ml}$, respectively), and it was shown to induce apoptosis in PC-3 and prostate cancer DU-145 cell lines, but not in CHO cells or human primary fibroblast cultures. *In vivo* in nude mice bearing human prostate cancer PC-3, once-daily treatment with compound (5 $\mu\text{g/kg}$ s.c. for 34 days) caused a significant reduction in tumor growth, and was not accompanied by evident toxicity. A good pharmacokinetic profile was observed in rats, with slow clearance from blood (30 ml/h/kg) and a long terminal half-life (22-29 h). Potentially useful for the treatment of hormone-refractory or end-stage prostate cancer.

SOURCE – Procyon.

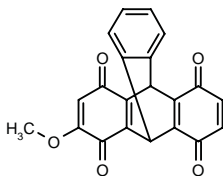
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- Liu, A.Y. et al. Decreased expression of prostatic secretory protein PSP-94 in prostate cancer. Cancer Lett 1993, 74(1-2): 91.
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TT-2

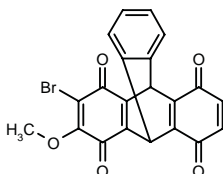
281968

3-Methoxy-1,4,5,8,9,10-hexahydro-9,10[1',2']-benzo-anthracene-1,4,5,8-tetraone



C21 H12 O5; Mol wt: 344.3208

ACTION – Antineoplastic agent proven to inhibit murine leukemia L1210 cell proliferation (IC_{50} = 300 and 150 nM, respectively, at days 2 and 4) and viability (IC_{50} = 250 and 100 nM, respectively, at days 2 and 4). Compound was found to inhibit DNA, RNA and protein synthesis (IC_{50} = 6 μ M) and cellular nucleoside transport (IC_{50} = 6 μ M), and to induce DNA cleavage, effects which were irreversible upon drug removal, suggesting that it may rapidly interact with several molecular targets in cell membranes and nuclei to disrupt the function of nucleoside transporters and nucleic acids. Potentially useful for enhancing the action of antimetabolites and sensitizing multidrug-resistant tumor cells in polychemotherapy. Another triptycene is:



TT-13 [281969]: C21 H11 Br O5

SOURCE – Kansas State University, Manhattan, KS (US).

REFERENCES

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CANCER GENE THERAPY

ISIS-16518

281330

Phosphorothioate oligonucleotide whose sequence is: 5'-AGCTTCTTTGCACATGTAAA-3', in which all residues are 2'-deoxy, except residues A, G, T, T, T, G, T, A, A and A in positions 1, 2, 4, 5, 15, 16, 17, 18, 19 and 20, which are 2'-methoxyethoxy-substituted, and C in positions 3 and 6 are 2'-methoxyethoxy-5-methylcytidines

ACTION – Antisense phosphorothioate oligonucleotide for modulating the expression of human mdm2, a gene implicated in abnormal cell proliferation and tumor formation. Compound was shown to inhibit mdm2 mRNA levels in human lung carcinoma A549 cells (82 and 91% inhibition at 50 and 200 nM, respectively), inhibit A549 cell proliferation (83% inhibition following 72-h exposure at a

concentration of 400 nM) and increase p53 protein levels (289% of control value [100%] at 300 nM). Other antisense oligonucleotides targeted to human mdm2 include the following:

Phosphorothioate oligonucleotide whose sequence is: 5'-TCTTTCCGACACACAGGGCC-3', in which all residues are 2'-deoxy, except residues T, T, T, T, A, G, G and G in positions 1, 3, 4, 5, 15, 16, 17 and 18, which are 2'-methoxyethoxy-substituted, and C in positions 2, 6, 19 and 20 are 2'-methoxyethoxy-5-methylcytidines

ISIS-16507 [281331]

Phosphorothioate oligonucleotide whose sequence is: 5'-GGTCTACCCTCCAATCGCCA-3', in which all C residues are 5-methylcytidines and all residues are 2'-deoxy, except residues G, G, T, C, T, A, T, C, G, C, C, C and A in positions 1, 2, 3, 4, 5, 6, 15, 16, 17, 18, 19 and 20, which are 2'-methoxyethoxy-substituted

ISIS-21927 [281332]

SOURCE – Isis Pharmaceuticals.

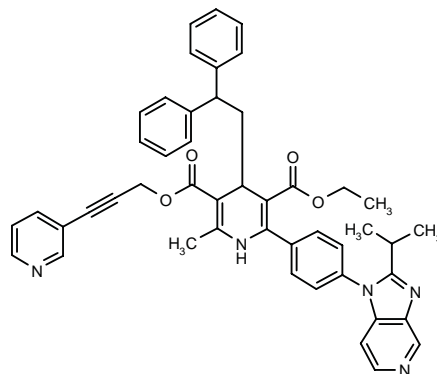
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

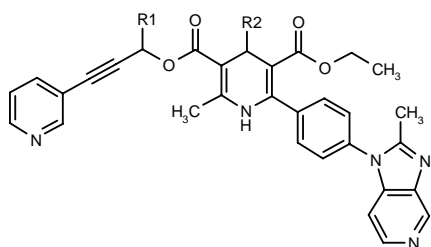
282013

4-(2,2-Diphenylethyl)-2-methyl-6-[4-(2-isopropyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylic acid 5-ethyl 3-[3-(3-pyridinyl)prop-2-ynyl] diester



C47 H43 N5 O4; Mol wt: 741.8877

ACTION – Multidrug resistance (MDR) modifier, a dihydropyridine derivative shown to reverse doxorubicin resistance *in vitro* in VJ-300 cells. *In vivo*, it significantly enhanced the antitumor activity of etoposide (VP-16; 3 mg/kg/day i.v. x 5 days) in vincristine-resistant leukemia P388-bearing mice when given at 10 or 20 mg/kg/day i.v. x 5 days. Other compounds from this series of 1,4-dihydropyridine derivatives include the following:



Compound	R1	R2	Formula
282017	H	(4-F-Ph) ₂ CHCH ₂	C ₄₅ H ₃₇ F ₂ N ₅ O ₄
282018	Me	CH ₂ CH ₂ Ph	C ₄₀ H ₃₇ N ₅ O ₄
282019	H	CH=CHPh	C ₃₉ H ₃₃ N ₅ O ₄
282020	H	CH ₂ Ph	C ₃₈ H ₃₃ N ₅ O ₄

SOURCE – Nikken Chemicals.

REFERENCES

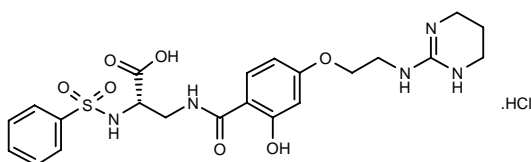
1. Tasaka, S. et al. (Nikken Chemicals Co., Ltd.) 1,4-Dihydropyridine derivs. WO 9941250.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

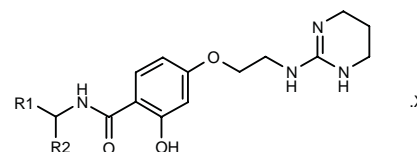
282147

3-[2-Hydroxy-4-[2-(1,4,5,6-tetrahydro-2-pyrimidinyl-amino)ethoxy]benzamido]-2(S)-(phenylsulfonamido)-propionic acid hydrochloride



C₂₂ H₂₇ N₅ O₇ S . HCl; Mol wt: 542.0102

ACTION – Selective vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist proven active in the osteopontin- $\alpha_v\beta_3$ cell attachment assay (IC_{50} = 0.002 μ M) and the osteoclast pitting assay for bone resorption inhibition (IC_{50} = 0.43 μ M). It was also effective in a model of parathyroid hormone (PTH)-induced hypercalcemia in thyroparathyroidectomized male rats. Potentially useful for the treatment of cancer, angiogenesis, restenosis, inflammation, bone diseases and viral infections, among other conditions. Other exemplified acylresorcinol derivatives include the following:



Compound	R1	R2	X	Formula
282148	(S)-CH(CO ₂ Et)NHCO ₂ Ph	H	HCl	C ₂₄ H ₃₁ N ₅ O ₇ S.HCl
282151	(S)-CH(CO ₂ Et)NHCO ₂ CH ₂ Ph	H	HCl	C ₂₆ H ₃₃ N ₅ O ₇ .HCl
282152	CH ₂ CO ₂ Et	Ph		C ₂₄ H ₃₀ N ₄ O ₅

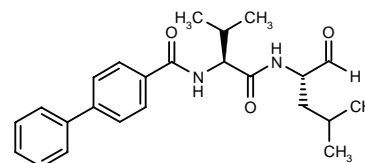
SOURCE – American Home Products.

REFERENCES

1. Kees, K.L. et al. (American Home Products Corp.) Acylresorcinol derivs. as selective vitronectin receptor inhibitors. WO 9952879.

282987

N-(Biphenyl-4-ylcarbonyl)-L-valyl-L-leucinal



C₂₄ H₃₀ N₂ O₃; Mol wt: 394.5120

ACTION – Cysteine protease inhibitor with potent inhibitory activity against cathepsins B, L, S and K, potentially useful for the treatment of osteoporosis, rheumatoid arthritis and muscular dystrophy.

SOURCE – Senju.

REFERENCES

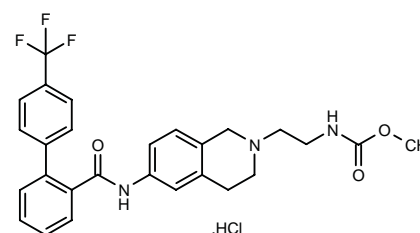
1. Nagao, Y. et al. Synthetic development of new peptidyl aldehyde derivatives having inhibitory activity against cysteine proteases. 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 1P-13.

TREATMENT OF LIPOPROTEIN DISORDERS

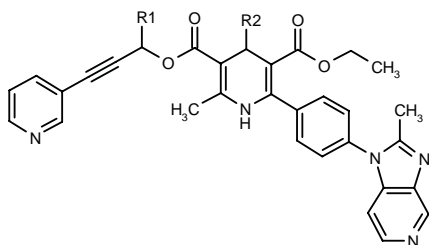
CP-467688*,1,3

266912

N-[2-[6-[4'-(Trifluoromethyl)biphenyl-2-ylcarboxamido]-1,2,3,4-tetrahydroisoquinolin-2-yl]ethyl]carbamic acid methyl ester hydrochloride



C₂₇ H₂₆ F₃ N₃ O₃ . HCl; Mol wt: 533.9753



Compound	R1	R2	Formula
282017	H	(4-F-Ph)2CHCH2	C ₄₅ H ₃₇ F ₂ N ₅ O ₄
282018	Me	CH2CH2Ph	C ₄₀ H ₃₇ N ₅ O ₄
282019	H	CH=CHPh	C ₃₉ H ₃₃ N ₅ O ₄
282020	H	CH2Ph	C ₃₈ H ₃₃ N ₅ O ₄

SOURCE – Nikken Chemicals.

REFERENCES

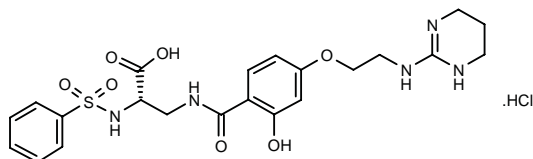
1. Tasaka, S. et al. (Nikken Chemicals Co., Ltd.) 1,4-Dihydropyridine derivs. WO 9941250.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

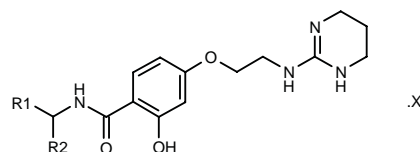
282147

3-[2-Hydroxy-4-[2-(1,4,5,6-tetrahydro-2-pyrimidinyl-amino)ethoxy]benzamido]-2(S)-(phenylsulfonamido)-propionic acid hydrochloride



C₂₂ H₂₇ N₅ O₇ S . HCl; Mol wt: 542.0102

ACTION – Selective vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist proven active in the osteopontin- $\alpha_v\beta_3$ cell attachment assay (IC_{50} = 0.002 μ M) and the osteoclast pitting assay for bone resorption inhibition (IC_{50} = 0.43 μ M). It was also effective in a model of parathyroid hormone (PTH)-induced hypercalcemia in thyroparathyroidectomized male rats. Potentially useful for the treatment of cancer, angiogenesis, restenosis, inflammation, bone diseases and viral infections, among other conditions. Other exemplified acylresorcinol derivatives include the following:



Compound	R1	R2	X	Formula
282148	(S)-CH(CO ₂ Et)NHSO ₂ Ph	H	HCl	C ₂₄ H ₃₁ N ₅ O ₇ S.HCl
282151	(S)-CH(CO ₂ Et)NHCO ₂ CH ₂ Ph	H	HCl	C ₂₆ H ₃₃ N ₅ O ₇ .HCl
282152	CH ₂ CO ₂ Et	Ph		C ₂₄ H ₃₀ N ₄ O ₅

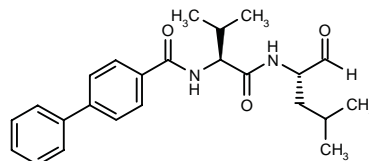
SOURCE – American Home Products.

REFERENCES

1. Kees, K.L. et al. (American Home Products Corp.) Acylresorcinol derivs. as selective vitronectin receptor inhibitors. WO 9952879.

282987

N-(Biphenyl-4-ylcarbonyl)-L-valyl-L-leucinal



C₂₄ H₃₀ N₂ O₃; Mol wt: 394.5120

ACTION – Cysteine protease inhibitor with potent inhibitory activity against cathepsins B, L, S and K, potentially useful for the treatment of osteoporosis, rheumatoid arthritis and muscular dystrophy.

SOURCE – Senju.

REFERENCES

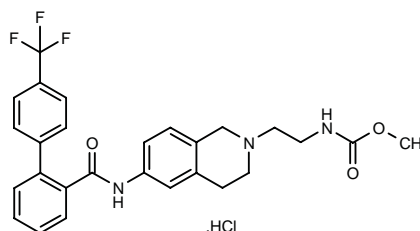
1. Nagao, Y. et al. Synthetic development of new peptidyl aldehyde derivatives having inhibitory activity against cysteine proteases. 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 1P-13.

TREATMENT OF LIPOPROTEIN DISORDERS

CP-467688*,1,3

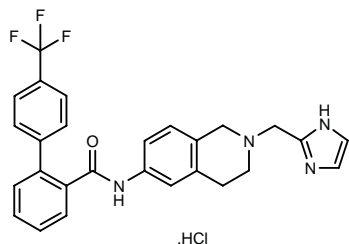
266912

N-[2-[6-[4'-(Trifluoromethyl)biphenyl-2-ylcarboxamido]-1,2,3,4-tetrahydroisoquinolin-2-yl]ethyl]carbamic acid methyl ester hydrochloride



C₂₇ H₂₆ F₃ N₃ O₃ . HCl; Mol wt: 533.9753

ACTION – Agent for the treatment of atherosclerosis, pancreatitis, obesity, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia and diabetes, an inhibitor of microsomal triglyceride transfer protein (MTP) and/or apolipoprotein B (Apo B) secretion. Pharmacokinetic studies in rats (5 mg/kg i.v. and 50 mg/kg p.o.) and dogs (2.5 mg/kg i.v. or p.o.) demonstrated favorable pharmacokinetic properties with high AUC in dogs after oral administration. The related compound **CP-319340** is also described:



CP-319340 [282535]^{2,3}: C₂₇ H₂₃ F₃ N₄ O . HCl

SOURCE – Pfizer.

REFERENCES

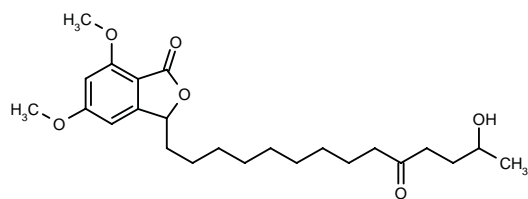
1. Chang, G. and Quallich, G.J. (Pfizer Inc.) *Apo B-secretion/MTP inhibitory amides*. EP 944602, WO 9823593.
2. Chang, G. et al. (Pfizer Inc.) *Biphenyl-2-carboxylic acid-tetrahydro-isoquinolin-6-yl amide derivs., their preparation and their use as inhibitors of microsomal triglyceride transfer protein and/or apolipoprotein B (Apo B) secretion*. JP 1999514964, US 5919795, WO 9640640.
3. Thornton-Manning, J.R. et al. *Pharmacokinetics of the microsomal triglyceride transfer protein (MTP) inhibitors CP-467,688 and CP-319,340 in preclinical species*. Annu Meet Am Assoc Pharm Sci (Nov 14-18, New Orleans) 1999, Abst 2489.

*Identified compound **266912** (see **266179**) Drug Data Rep 1998, 020(08): 0678.

MD-700

264774

3-(13-Hydroxy-10-oxotetradecyl)-5,7-dimethoxy-1(3H)-isobenzofuranone



C₂₄ H₃₆ O₆; Mol wt: 420.5424

ACTION – Hypocholesterolemic agent able to increase the expression of LDL receptor mRNA in HepG2 cells in a concentration-dependent manner (0.03-0.1 µg/ml). Compound produced a time- and concentration-dependent increase in the uptake of labeled LDL and of luciferase activity in HepG2 cells transiently transfected with promoter-luciferase gene constructs, indicating that it stimulates LDL receptor mRNA expression via transcriptional induction of the LDL receptor gene. In hamsters, it induced a significant increase in maximal [¹²⁵I]-labeled

LDL binding to liver membranes without modifying binding affinity and, in contrast to pravastatin, it had no effect on cholesterol synthesis in liver homogenates. Hamsters fed a normal diet and treated with compound (0.3 mg/kg/day for 10 days) showed a significant decrease in total serum cholesterol levels (18%), whereas pravastatin at the same dose produced a nonsignificant 14% decrease, and this effect was shown to be due to a selective reduction in LDL and VLDL cholesterol. Compound also significantly reduced total serum cholesterol levels in hamsters and rats fed a hypercholesterolemic diet at respective doses of 15-45 mg/kg and 40 mg/kg orally for 3 days. Compound thus appears to lower serum cholesterol, independently of an effect on cholesterol synthesis or cholesterol absorption, via enhanced hepatic LDL receptor expression at the transcriptional level.

SOURCE – Taisho.

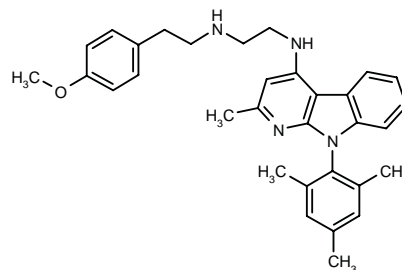
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1. Adachi, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Isobenzofuranone cpd. and lipid lowering agent*. JP 1996151375, WO 9610020.
2. Murakami, S. et al. *Increase in LDL uptake and receptor number by a novel isobenzofuranone, MD-700*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 50.
3. Murakami, S. et al. *Up-regulation of low density lipoprotein receptor by a novel isobenzofuranone derivative, MD-700*. *Atherosclerosis* 1999, 146(2): 281.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

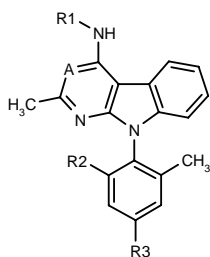
281934

N-[2-(4-Methoxyphenyl)ethyl]-N-[2-[2-methyl-9-(2,4,6-trimethylphenyl)-9H-pyrido[2,3-b]indol-4-ylamino]ethyl]-amine



C₃₂ H₃₆ N₄ O; Mol wt: 492.6634

ACTION – Agent for the treatment of disorders characterized by excess neuropeptide Y (NPY) such as eating disorders including obesity and bulimia, and cardiovascular diseases including essential hypertension and congestive heart failure, that selectively binds Y₁ receptors. Other specifically claimed compounds within this series of substituted 9H-pyrido[2,3-b]indole and 9H-pyrimido[4,5-b]indole derivatives include the following:



Compound	R1	R2	R3	A	Formula
281935	COCH ₂ N(Me) ₂	Me	Me	CH	C ₂₅ H ₂₈ N ₄ O
281936	cyclopropyl-CH ₂ NHCH ₂ CH ₂	Me	Me	N	C ₂₆ H ₃₁ N ₅
281937	4-(cyclopentyl-O)-3-MeO-Ph-CH ₂ CH ₂ NHCH ₂ CH ₂	Me	Me	CH	C ₃₇ H ₄₄ N ₄ O ₂
281938	CH ₂ CH ₂ NHEt	H	Cl	N	C ₂₂ H ₂₄ ClN ₅
281939	CH ₂ CONH ₂	Me	Me	N	C ₂₂ H ₂₃ N ₅ O
281940	cis-2-NH ₂ -cyclohexyl	Me	Me	N	C ₂₆ H ₃₁ N ₅

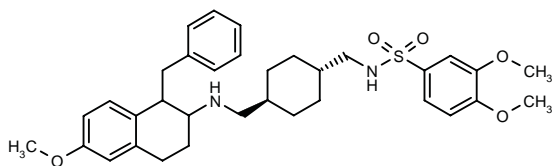
SOURCE – Neurogen.

REFERENCES

1. Darrow, J.W. et al. (Neurogen Corp.) *Substd. 9H-pyridino[2,3-b]indole and 9H-pyrimidino[4,5-b]indole derivs: Selective neuropeptide Y receptor ligands*. WO 9951598.

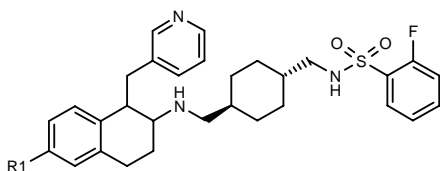
282629

N-[*trans*-4-(1-Benzyl-6-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylaminomethyl)cyclohexylmethyl]-3,4-dimethoxybenzenesulfonamide



C34 H44 N2 O5 S; Mol wt: 592.7966

ACTION – Neuropeptide Y (NPY) Y₅ receptor ligand (100% inhibition of [¹²⁵I]-PYY binding in HEK293 cells transfected with the human Y₅ receptor at 3 μM) proven to reduce food intake in food-deprived rats (40.2% reduction at 6 h after administration of 30 mg/kg i.p.). Potentially useful for the treatment of obesity, bulimia nervosa, diabetes, dyslipidemia, hypertension, memory loss, epileptic seizures, migraine, sleep disturbances, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea. Other compounds from this series of *N*-substituted aminotetralins include the following:



Compound	R1	Formula
282630	F	C ₃₀ H ₃₅ F ₂ N ₃ O ₂ S
282631	OMe	C ₃₁ H ₃₈ FN ₃ O ₃ S
282632	OH	C ₃₀ H ₃₈ FN ₃ O ₃ S

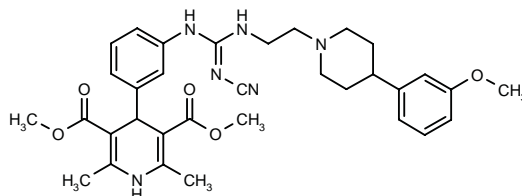
SOURCE – Ortho-McNeil.

REFERENCES

1. Dax, S.L. et al. (Ortho-McNeil Pharmaceutical, Inc.) *N-Substd. aminotetralins as ligands for the neuropeptide Y Y5 receptor useful in the treatment of obesity and other disorders*. WO 9955667.

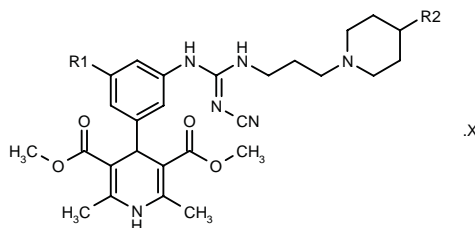
284056

4-[3-[*N*³-Cyano-*N*²-[2-[4-(3-methoxyphenyl)piperidin-1-yl]ethyl]guanidino]phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl diester



C33 H40 N6 O5; Mol wt: 600.7160

ACTION – Neuropeptide Y (NPY) antagonist for use in the treatment of eating disorders such as obesity. It possesses good Y₁ receptor-antagonist activity and reduced cardiovascular effects. Other specifically claimed dihydropyridine derivatives include the following:



Compound	R1	R2	X	Formula
284057	H	3-OH-Ph	maleate	C ₃₃ H ₄₀ N ₆ O ₅ ·C ₄ H ₄ O ₄
284058	H	3-N(Me) ₂ -Ph		C ₃₅ H ₄₅ N ₇ O ₄
284059	I	Ph		C ₃₃ H ₃₉ N ₆ O ₄
284060	H	Et		C ₂₉ H ₄₀ N ₆ O ₄
284061	H	t-Bu		C ₃₁ H ₄₄ N ₆ O ₄

SOURCE – Bristol-Myers Squibb.

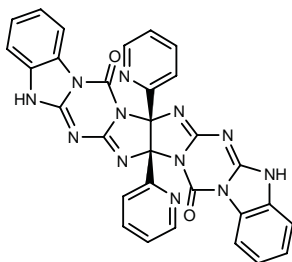
REFERENCES

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HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

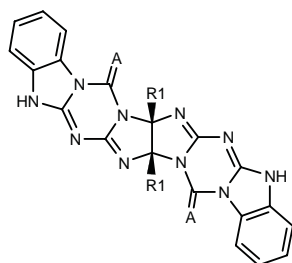
283896

7a(S),17a(S)-Di(pyridin-2-yl)-5,7a,9,15,17a,19-hexahydrobenzimidazo[2''',1''':4''',5''']-[1,3,5]triazino-[2''',1''':2'',3'']imidazo[4'',5'':4',5']imidazo[2',1':4,5][1,3,5]-triazino[1,2-a]benzimidazole-9,19-dione



C30 H18 N12 O2; Mol wt: 578.5542

ACTION – Granulocyte colony-stimulating factor (G-CSF) mimetic expected to be of utility in the treatment of neutropenia to enhance leukocyte production, as well as in the treatment of bacterial and fungal infections. Other specifically claimed octacyclic compounds are:



Compound	R1	A	Formula
283897	Ph	O	C ₃₂ H ₂₀ N ₁₀ O ₂
283898	4-F-Ph	O	C ₃₂ H ₁₈ F ₂ N ₁₀ O ₂
283899	4-Br-Ph	O	C ₃₂ H ₁₈ Br ₂ N ₁₀ O ₂
283900	2-Pyr	S	C ₃₀ H ₁₈ N ₁₂ S ₂

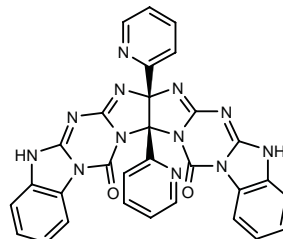
SOURCE – SmithKline Beecham.

REFERENCES

1. Duffy, K.J. and Luengo, J.I. (SmithKline Beecham Corp.) *G-CSF mimetics*. WO 9961445.

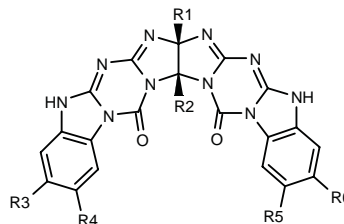
283901

7a,17a-Di(pyridin-2-yl)-5,7a,10,16,17a,19-hexahydrobenzimidazo[2''',1''':4''',5''']-[1,3,5]triazino-[1''',2''':1'',2'']imidazo[4'',5'':4',5']imidazo[2',1':4,5][1,3,5]-triazino[1,2-a]benzimidazole-16,19-dione



C30 H18 N12 O2; Mol wt: 578.5542

ACTION – Granulocyte colony-stimulating factor (G-CSF) mimetic expected to be of utility in the treatment of neutropenia to enhance leukocyte production, as well as in the treatment of bacterial and fungal infections. Other specifically claimed octacyclic compounds are:



Compound	R1=R2	R3	R4	R5	R6	Formula
283902	Ph	H	H	H	H	C ₃₂ H ₂₀ N ₁₀ O ₂
283903	4-F-Ph	H	H	H	H	C ₃₂ H ₁₈ F ₂ N ₁₀ O ₂
283904	3-MeO-Ph	H	H	H	H	C ₃₄ H ₂₄ N ₁₀ O ₄
283905	2-Pyr	NO ₂	H	H	NO ₂	C ₃₀ H ₁₆ N ₁₄ O ₆
283906	2-Pyr	H	NO ₂	H	NO ₂	C ₃₀ H ₁₆ N ₁₄ O ₆
283907	2-Pyr	H	NO ₂	NO ₂	H	C ₃₀ H ₁₆ N ₁₄ O ₆

SOURCE – SmithKline Beecham.

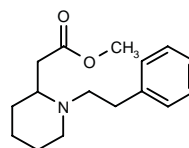
REFERENCES

1. Duffy, K.J. and Luengo, J.I. (SmithKline Beecham Corp.) *G-CSF mimetics*. WO 9961446.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

283029

2-[1-(2-Phenylethyl)piperidin-2-yl]acetic acid methyl ester

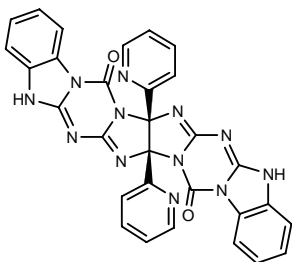


C16 H23 N O2; Mol wt: 261.3627

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

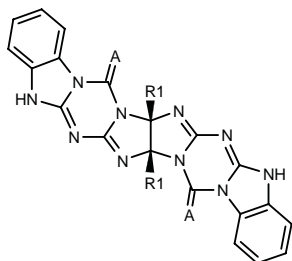
283896

7a(S), 17a(S)-Di(pyridin-2-yl)-5,7a,9,15,17a,19-hexahydrobenzimidazo[2''',1''':4''',5''']-[1,3,5]triazino[2''',1''':2'',3'']imidazo[4'',5'':4',5']imidazo[2',1':4,5][1,3,5]-triazino[1,2-a]benzimidazole-9,19-dione



C30 H18 N12 O2; Mol wt: 578.5542

ACTION – Granulocyte colony-stimulating factor (G-CSF) mimetic expected to be of utility in the treatment of neutropenia to enhance leukocyte production, as well as in the treatment of bacterial and fungal infections. Other specifically claimed octacyclic compounds are:



Compound	R1	A	Formula
283897	Ph	O	C ₃₂ H ₂₀ N ₁₀ O ₂
283898	4-F-Ph	O	C ₃₂ H ₁₈ F ₂ N ₁₀ O ₂
283899	4-Br-Ph	O	C ₃₂ H ₁₈ Br ₂ N ₁₀ O ₂
283900	2-Pyr	S	C ₃₀ H ₁₈ N ₁₂ S ₂

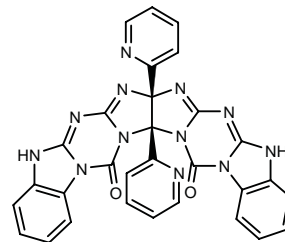
SOURCE – SmithKline Beecham.

REFERENCES

1. Duffy, K.J. and Luengo, J.I. (SmithKline Beecham Corp.) *G-CSF mimetics*. WO 9961445.

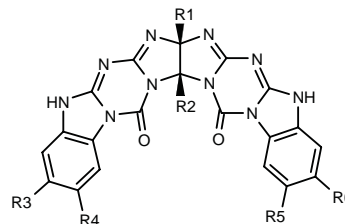
283901

7a, 17a-Di(pyridin-2-yl)-5,7a,10,16,17a,19-hexahydrobenzimidazo[2''',1''':4''',5''']-[1,3,5]triazino[1''',2''':1'',2'']imidazo[4'',5'':4',5']imidazo[2',1':4,5][1,3,5]-triazino[1,2-a]benzimidazole-16,19-dione



C30 H18 N12 O2; Mol wt: 578.5542

ACTION – Granulocyte colony-stimulating factor (G-CSF) mimetic expected to be of utility in the treatment of neutropenia to enhance leukocyte production, as well as in the treatment of bacterial and fungal infections. Other specifically claimed octacyclic compounds are:



Compound	R1=R2	R3	R4	R5	R6	Formula
283902	Ph	H	H	H	H	C ₃₂ H ₂₀ N ₁₀ O ₂
283903	4-F-Ph	H	H	H	H	C ₃₂ H ₁₈ F ₂ N ₁₀ O ₂
283904	3-MeO-Ph	H	H	H	H	C ₃₄ H ₂₄ N ₁₀ O ₄
283905	2-Pyr	NO ₂	H	H	NO ₂	C ₃₀ H ₁₆ N ₁₄ O ₆
283906	2-Pyr	H	NO ₂	H	NO ₂	C ₃₀ H ₁₆ N ₁₄ O ₆
283907	2-Pyr	H	NO ₂	NO ₂	H	C ₃₀ H ₁₆ N ₁₄ O ₆

SOURCE – SmithKline Beecham.

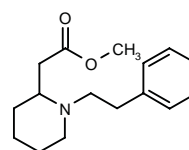
REFERENCES

1. Duffy, K.J. and Luengo, J.I. (SmithKline Beecham Corp.) *G-CSF mimetics*. WO 9961446.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

283029

2-[1-(2-Phenylethyl)piperidin-2-yl]acetic acid methyl ester



C16 H23 N O2; Mol wt: 261.3627

ACTION – Agent with potential in the treatment of cocaine abuse, a modified methylphenidate analogue that is able to bind to the cocaine binding site on the dopamine transporter (DAT; $IC_{50} = 2.24 \mu M$ for inhibition of [3H]-Win-35428 binding in rat striatal tissue); compound was 27-fold less potent than methylphenidate but showed a wider separation between potency against dopamine uptake versus DAT binding (3.9-fold vs. 2.7-fold).

SOURCES – Georgia Institute of Technology, Atlanta, GA (US); Mercer University, Atlanta, GA (US).

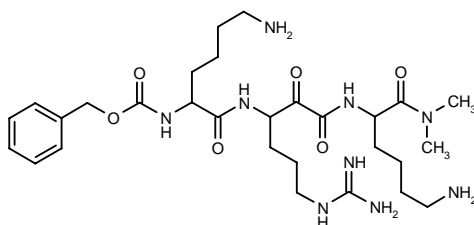
REFERENCES

1. Deutsch, H.M. et al. *Synthesis and pharmacology of site-specific cocaine abuse treatment agents: The role of the phenyl group in highly modified methylphenidate analogs as dopamine uptake inhibitors*. Med Chem Res 1999, 9(4): 213.
2. Schweri, M.M. et al. *Synthesis and pharmacology of desphenyl methylphenidate derivatives as potential cocaine abuse treatment agents*. Soc Neurosci Abst 1999, 25(Part 1): Abst 66.10.

DENTAL AGENTS

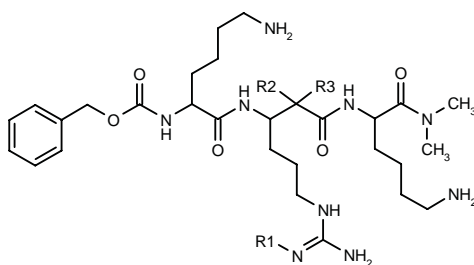
282064

N^2 -Benzyloxycarbonyl-DL-lysyl-DL-arginylcarbonyl-DL-lysine dimethylamide



C29 H49 N9 O6; Mol wt: 619.7631

ACTION – Agent for the treatment or prevention of periodontitis that selectively inhibits the protein-degrading activity of gingipain R (Arg-gingipain, argingipain, gingipain 1), as demonstrated by IC_{50} values of 0.84, 140 and 120 nM against gingipain R and cathepsin B and L, respectively. Other exemplified compounds from this series of peptide derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
282066	H	OH	H	A	$C_{29}H_{51}N_9O_6$
284067	H	H	OH	B	$C_{29}H_{51}N_9O_6$
282069	NO ₂	-O-			$C_{29}H_{48}N_{10}O_8$

SOURCE – Taiho.

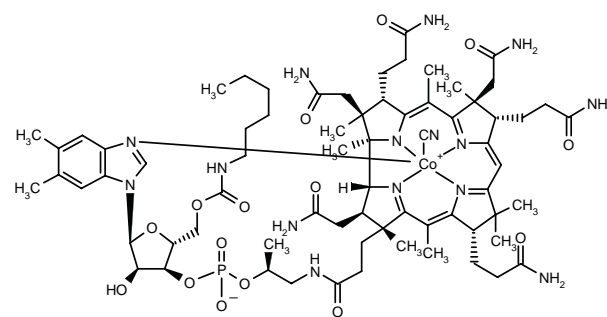
REFERENCES

1. Yamamoto, K. et al. (Taiho Pharmaceutical Co., Ltd.) *Peptide derivs. and their pharmaceutically acceptable salts, their preparation method, and use*. JP 199928526.

DRUG DELIVERY

284601

5'-O-(N-Hexylcarbamoyle)vitamin B₁₂



C70 H101 Co N15 O15 P; Mol wt: 1482.5650

ACTION – Vitamin B₁₂ derivative suitable for linking to a polymer, nanoparticle or therapeutic agent for use as a carrier molecule thereof.

SOURCE – Biotech Australia.

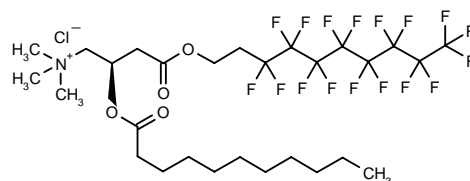
REFERENCES

1. Russell-Jones, G. and McEwan, J. (Biotech Australia Pty Ltd.) *Vitamin B₁₂ derivs. and methods for their preparation*. WO 9965930.

ST-1223

282801

N -[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Hepta-decafluorodecyloxy)-4-oxo-2(R)-(undecanoyloxy)butyl]- N,N,N -trimethylammonium chloride



C28 H39 Cl F17 N O4; Mol wt: 812.0381

ACTION – Perfluorinated ester of alkanoyl L-carnitine, useful for the preparation of cationic liposomes suitable for the intracellular delivery of pharmacologically active compounds, preferably genes, facilitating their trans-membrane transport, or for promoting their interaction with specific receptors. Other specifically claimed compounds are:

ACTION – Agent with potential in the treatment of cocaine abuse, a modified methylphenidate analogue that is able to bind to the cocaine binding site on the dopamine transporter (DAT; $IC_{50} = 2.24 \mu M$ for inhibition of [3H]-Win-35428 binding in rat striatal tissue); compound was 27-fold less potent than methylphenidate but showed a wider separation between potency against dopamine uptake versus DAT binding (3.9-fold vs. 2.7-fold).

SOURCES – Georgia Institute of Technology, Atlanta, GA (US); Mercer University, Atlanta, GA (US).

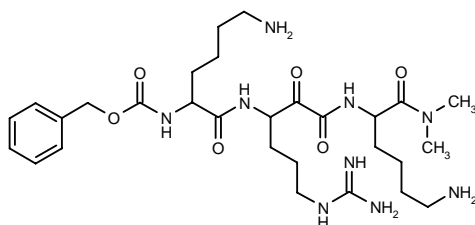
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DENTAL AGENTS

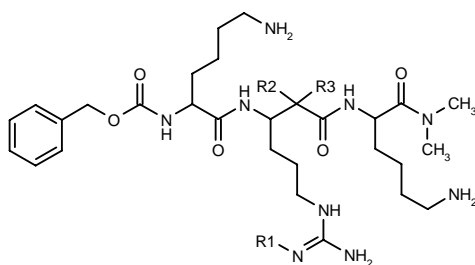
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282069	NO ₂	-O-			C ₂₉ H ₄₈ N ₁₀ O ₈

SOURCE – Taiho.

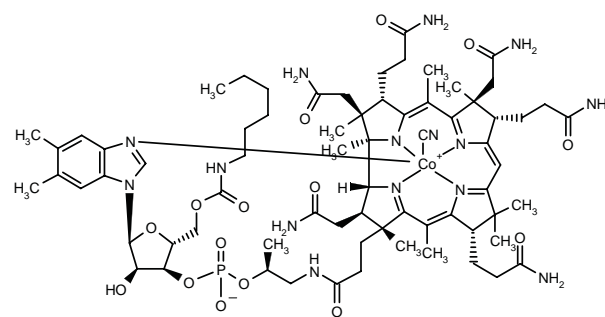
REFERENCES

1. Yamamoto, K. et al. (Taiho Pharmaceutical Co., Ltd.) *Peptide derivs. and their pharmaceutically acceptable salts, their preparation method, and use*. JP 1999228526.

DRUG DELIVERY

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SOURCE – Biotech Australia.

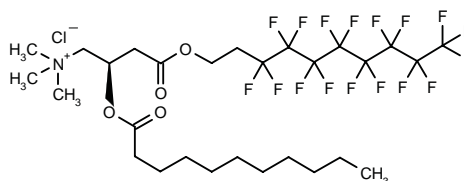
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ST-1223

282801

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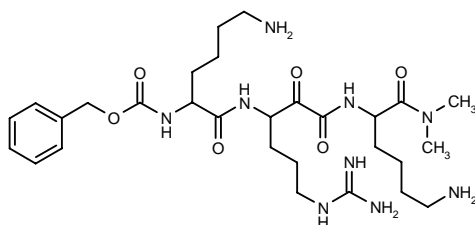
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DENTAL AGENTS

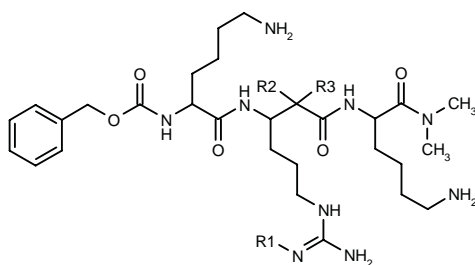
282064

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282069	NO ₂	-O-			C ₂₉ H ₄₈ N ₁₀ O ₈

SOURCE – Taiho.

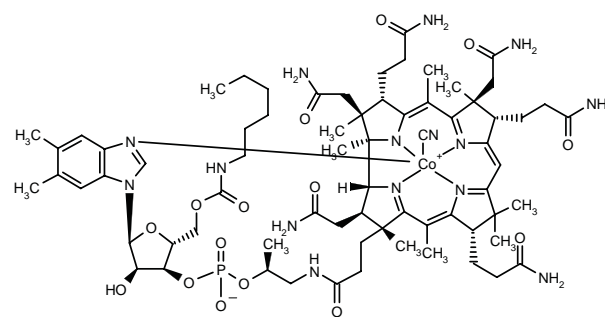
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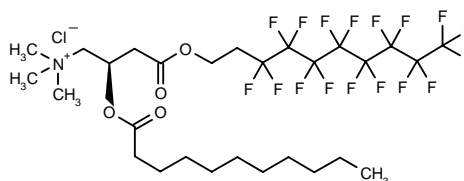
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ST-1223

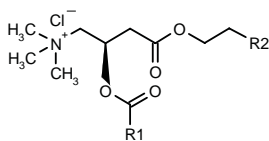
282801

N-[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Hepta-decafluorodecyloxy)-4-oxo-2-(*R*)-(undecanoyloxy)butyl]-*N,N,N*-trimethylammonium chloride



C28 H39 Cl F17 N O4; Mol wt: 812.0381

ACTION – Perfluorinated ester of alkanoyl L-carnitine, useful for the preparation of cationic liposomes suitable for the intracellular delivery of pharmacologically active compounds, preferably genes, facilitating their trans-membrane transport, or for promoting their interaction with specific receptors. Other specifically claimed compounds are:



Compound	R1	R2	Formula
ST-1221 [282802]	C11H23	(CF2)5CF3	C ₂₇ H ₄₁ ClF ₁₃ NO ₄
ST-1245 [282803]	C11H23	CH2CF2CF3	C ₂₄ H ₄₃ ClF ₅ NO ₄
ST-1246 [282804]	C10H21	(CF2)3CF3	C ₂₄ H ₃₉ ClF ₉ NO ₄
ST-1192 [282805]	i-Bu	(CH2)4(CF2)3CF3	C ₂₂ H ₃₅ ClF ₉ NO ₄
ST-1193 [282806]	C10H21	(CH2)4(CF2)3CF3	C ₂₈ H ₄₇ ClF ₉ NO ₄

SOURCE – Sigma-Tau.

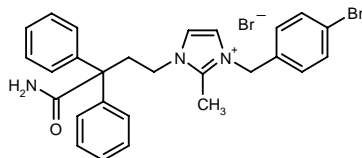
REFERENCES

1. Santaniello, M. et al. (Sigma-Tau Industrie Farmaceutiche Riunite SpA) *Perfluorinated esters of alkanoyl L-carnitine for the preparation of cationic lipids for the intracellular delivery of pharmacologically active cpds.* WO 9957094.

PHARMACOLOGICAL TOOLS

282062

1-(3-Carbamoyl-3,3-diphenylpropyl)-3-(4-bromobenzyl)-2-methyl-1*H*-imidazol-3-ium bromide



C₂₇ H₂₇ Br₂ N₃ O; Mol wt: 569.3383

ACTION – Potent and selective muscarinic M₃ receptor antagonist ($K_b = 0.117$ nM) with 22-fold selectivity versus M₂ receptors ($K_b = 2.58$ nM). Compound is more potent and selective than 4-DAMP and the parent compound KRP-197⁺ and may be useful as a pharmacological tool to study muscarinic acetylcholine receptor localization and internalization, and also as a peripherally selective muscarinic antagonist.

SOURCE – Kyorin.

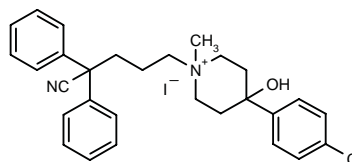
REFERENCES

1. Miyachi, H. et al. (Kyorin Pharmaceutical Co., Ltd.) *Novel imidazole deriv. and process for producing the same.* EP 733621, US 5932607, WO 9515951.
2. Miyachi, H. et al. *Design, synthesis and antimuscarinic activity of some imidazolium derivatives.* Bioorg Med Chem Lett 1999, 9(20): 3003.

*Drug Data Rep 1998, 020(09): 0778.

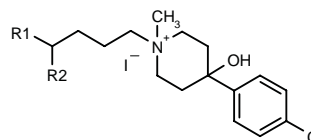
282195

4-(4-Chlorophenyl)-1-(4-cyano-4,4-diphenylbutyl)-4-hydroxy-1-methylpiperidinium iodide



C₂₉ H₃₂ Cl I N₂ O; Mol wt: 586.9378

ACTION – Potent and selective human chemokine CCR1 receptor antagonist ($K_i = 8$ nM for displacement of [¹²⁵I]-MIP-1 α binding from human CCR1 receptors expressed in HEK293 cells), with potent functional antagonist activity in the inhibition of MIP-1 α -induced intracellular calcium mobilization in HEK293 cells ($IC_{50} = 1.8$ μ M). This and the other quaternary ammonium salts shown below are reported to have poor oral absorption and rapid clearance *in vivo*, making them unsuitable as drug candidates, but they are potentially useful as tools to elucidate the physiopharmacology of this receptor.



Compound	R1	R2	Formula
282196	Ph	Ph	C ₂₈ H ₃₃ ClINO
282197	CN	2-Naph	C ₂₇ H ₃₀ ClIN ₂ O

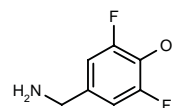
SOURCE – Berlex.

REFERENCES

1. Ng, H.P. et al. *Discovery of novel non-peptide CCR1 receptor antagonists.* J Med Chem 1999, 42(22): 4680.

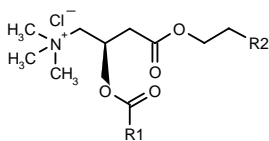
282752

4-(Aminomethyl)-2,6-difluorophenol



C₇ H₇ F₂ N O; Mol wt: 159.1343

ACTION – GABA_C receptor antagonist, as demonstrated in voltage clamp experiments in *Xenopus* oocytes transfected with human GABA_C receptors, where compound was seen to competitively inhibit the GABA-induced inward currents ($K_B = 75.5$ μ M); it has weak inhibitory activity on GABA_A receptors and little or no effect on GABA_B receptors. The good lipophilicity of the compound should facilitate penetration of the blood-brain barrier, allowing its use as a pharmacological tool to characterize brain GABA_C receptors.



Compound	R1	R2	Formula
ST-1221 [282802]	C11H23	(CF2)5CF3	C ₂₇ H ₄₁ ClF ₁₃ NO ₄
ST-1245 [282803]	C11H23	CH2CF2CF3	C ₂₄ H ₄₃ ClF ₉ NO ₄
ST-1246 [282804]	C10H21	(CF2)3CF3	C ₂₄ H ₃₉ ClF ₉ NO ₄
ST-1192 [282805]	i-Bu	(CH2)4(CF2)3CF3	C ₂₂ H ₃₅ ClF ₉ NO ₄
ST-1193 [282806]	C10H21	(CH2)4(CF2)3CF3	C ₂₈ H ₄₇ ClF ₉ NO ₄

SOURCE – Sigma-Tau.

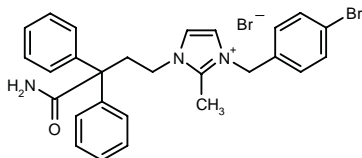
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PHARMACOLOGICAL TOOLS

282062

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SOURCE – Kyorin.

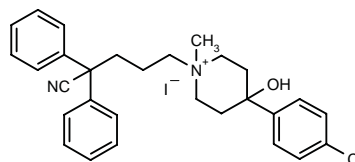
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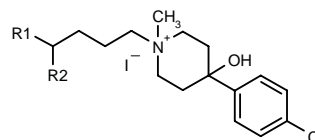
282195

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282197	CN	2-Naph	C ₂₇ H ₃₀ ClIN ₂ O

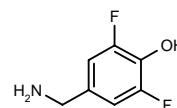
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282752

4-(Aminomethyl)-2,6-difluorophenol



C₇ H₇ F₂ N O; Mol wt: 159.1343

ACTION – GABA_C receptor antagonist, as demonstrated in voltage clamp experiments in *Xenopus* oocytes transfected with human GABA_C receptors, where compound was seen to competitively inhibit the GABA-induced inward currents (K_B = 75.5 μM); it has weak inhibitory activity on GABA_A receptors and little or no effect on GABA_B receptors. The good lipophilicity of the compound should facilitate penetration of the blood-brain barrier, allowing its use as a pharmacological tool to characterize brain GABA_C receptors.

SOURCE – AstraZeneca.

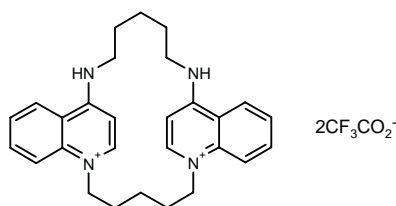
REFERENCES

1. Chebib, M. et al. *Aminomethyl-2,6-difluorophenols as a novel class of increased lipophilicity GABA_A receptor antagonists*. *Bioorg Med Chem Lett* 1999, 9(21): 3093.
2. Qiu, J. et al. *2,6-Difluorophenol as a bioisostere of a carboxylic acid: Bioisosteric analogues of gamma-aminobutyric acid*. *J Med Chem* 1999, 42(2): 329.

UCL-1848

283226

6,7,8,9,10,11,12,19,20,21,22,23-Dodecahydro-5,24:13,18-diethenodibenzo[*b,m*][1,5,11,15]tetraazacycloicosine-18,24-diium bis(trifluoroacetate)



C₂₈ H₃₄ N₄ . 2 C₂ F₃ O₂; Mol wt: 652.6326

ACTION – Potent, nonpeptide apamin-sensitive, small-conductance Ca²⁺-activated K⁺ (SK) channel blocker, as demonstrated by its ability to block the slow afterhyperpolarization (AHP) in rat superior cervical ganglion neurons (IC₅₀ = 2.7 nM). Compound appears to be highly selective for apamin-sensitive subtypes because it does not affect the I_K and SK1 channels in rabbit blood cells and hippocampal pyramidal neurons, respectively. It also potentially inhibited [¹²⁵I]-apamin binding in guinea pig hepatocytes with a K_i of 140 pM. Potentially useful as a tool for the study of both native and cloned apamin-sensitive SK channels.

SOURCE – University College London, London (GB).

REFERENCES

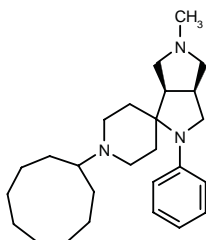
1. Campos-Rosa, J. et al. (University College London) *Potassium channel blockers*. WO 9748705.
2. Benton, D.C.H. et al. *UCL 1848: A novel bis-quinolinium cyclophane which blocks apamin-sensitive K⁺ channels with nanomolar affinity*. *Br J Pharmacol* 1999, 128(Suppl.): Abst 39P.

ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

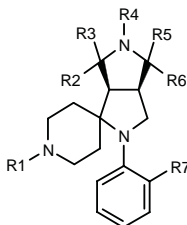
284253

(3'a*RS*,6'a*SR*)-1-Cyclononyl-5'-methyl-2'-phenylperhydrospiro[piperidine-4,1'-pyrrolo[3,4-*c*]pyrrole]



C₂₆ H₄₁ N₃; Mol wt: 395.6309

ACTION – Orphanin FQ (OFQ, nociceptin, ORL1) receptor modulator with potential in the treatment of anxiety, stress disorders, depression, trauma, memory impairment such as in Alzheimer's disease, epilepsy and convulsions, acute and chronic pain, symptoms of addictive drug withdrawal, for the control of water balance, Na⁺ excretion and arterial blood pressure, and for the treatment of metabolic disorders such as obesity. Other specifically claimed compounds from this series of spiro[piperidine-4,1'-pyrrolo[3,4-*c*]pyrrole] derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	Formula
284254	cis-4-i-Pr-cyclohexyl	H	H	Bu	H	H	H	C ₂₉ H ₄₇ N ₃
284256	cis-4-i-Pr-cyclohexyl	-O-		Me		-O-	H	C ₂₈ H ₃₇ N ₃ O ₂
284257	cis-4-i-Pr-cyclohexyl	H	H	CH ₂ CH ₂ OH	H	H	H	C ₂₇ H ₄₃ N ₃ O
284258	cyclodecyl	H	H	Me	H	H	F	C ₂₇ H ₄₂ FN ₃
284259	cyclodecyl	H	H	cyclopropyl-CO	H	H	H	C ₃₀ H ₄₅ N ₃ O

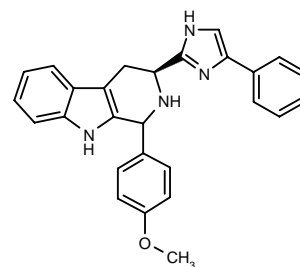
SOURCE – Roche.

REFERENCES

- Adam, G. et al. (F. Hoffmann-La Roche AG) *Spiro(piperidine-4,1'-pyrrolo[3,4-*c*]pyrrole)*. CA 2274201, CA 2274204, EP 0963987, JP 2000026466.

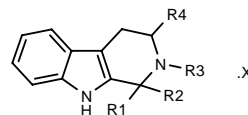
284304

1-(4-Methoxyphenyl)-3(*S*)-(4-phenyl-1*H*-imidazol-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole

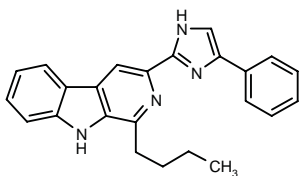


C₂₇ H₂₄ N₄ O; Mol wt: 420.5136

ACTION – Agent that binds to somatostatin receptors and blocks Na channels, with potential in the treatment of acromegaly, restenosis, Crohn's disease, diarrhea, irritable bowel syndrome, pancreatitis, gastroesophageal reflux, hyperparathyroidism, Graves' disease, diabetic neuropathy, cancer, adenomas, diabetes mellitus, nephropathy, peptic ulcers and *Helicobacter pylori*-related disorders, as well as neuropathic pain, arrhythmias, epilepsy and neuronal damage. A representative compound from a series of β-carboline derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	X	Isomer	Formula
284305	H	4-MeO-Ph	CONH-CH ₂ Ph	4-Ph-2-imidazolyl		S	C ₃₈ H ₃₁ N ₅ O ₂
284307	Bu	Bu	H	4,5-(Me) ₂ -2-oxazolyl	HCl	R	C ₂₄ H ₃₃ N ₃ O.HCl
284308	-(CH ₂) ₂ N(4-CF ₃ -Ph-NHCO)(CH ₂) ₂ -		H	4-Ph-2-imidazolyl		R	C ₃₂ H ₂₉ F ₃ N ₆ O



284306: C₂₄ H₂₂ N₄

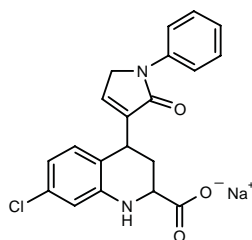
SOURCE – SCRAS.

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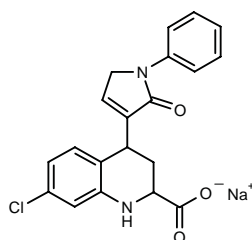
284324

(-)-7-Chloro-4-(2-oxo-1-phenyl-2,5-dihydro-1H-pyrrol-3-yl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid sodium salt

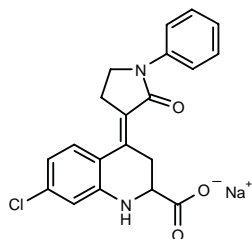


C₂₀ H₁₆ Cl N₂ Na O₃; Mol wt: 390.8004

ACTION – Agent for the treatment or prevention of neurotoxic damage, neurodegenerative diseases and pain, a selective antagonist at the strychnine-insensitive glycine binding site on the NMDA receptor complex. Antinociceptive activity was demonstrated in the formalin-induced paw-licking test in mice (ED₅₀ = 0.03 mg/kg p.o.). Other compounds from this series of tetrahydroquinoline derivatives include the following:



284326: C₂₀ H₁₆ Cl N₂ Na O₃; (+)-isomer



284327: C₂₀ H₁₄ Cl N₂ Na O₃; (-)-isomer

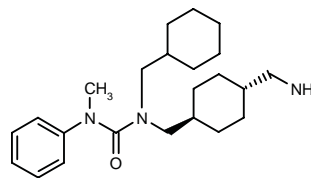
SOURCE – Glaxo Wellcome.

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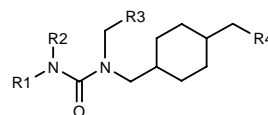
284749

trans-N-[4-(Aminomethyl)cyclohexylmethyl]-N-(cyclohexylmethyl)-N'-methyl-N'-phenylurea



C₂₃ H₃₇ N₃ O; Mol wt: 371.5653

ACTION – Agent for the treatment of pain, gastrointestinal disorders and spinal injuries, a selective δ-opioid receptor ligand. Other specifically claimed compounds within this series of 1,4-substituted cyclohexyl derivatives include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
284750	Me	Ph	cyclohexyl	NHC(=NH)NH ₂	trans	C ₂₄ H ₃₉ N ₅ O
284751	Me	Ph	4-Cl-Ph	NHC(=NH)NH ₂		C ₂₄ H ₃₂ ClN ₅ O
284752	-CH ₂ CH ₂ - OCH ₂ CH ₂ -		CH(Ph) ₂	NHC(=NH)NH ₂		C ₂₈ H ₃₉ N ₅ O ₂
284753	Me	Ph	1-Naph	NHC(=NH)NH ₂		C ₂₈ H ₃₅ N ₅ O
284754	Me	Ph	2-Naph	NHC(=NH)NH ₂		C ₂₈ H ₃₅ N ₅ O
284755	Me	Ph	cyclohexyl	3-pyridazinyl-NH	trans	C ₂₇ H ₃₉ N ₅ O
284756	Me	Ph	cyclohexyl	1-oxido-2-Pyr-NH	trans	C ₂₈ H ₄₀ N ₄ O ₂
284757	Me	Ph	cyclohexyl	NHC(NH ₂)=CHNO ₂	trans	C ₂₈ H ₃₉ N ₅ O ₃
284758	Me	Ph	cyclohexyl	3-NO ₂ -2-pyrrolyl-NH	trans	C ₂₇ H ₃₉ N ₅ O ₃

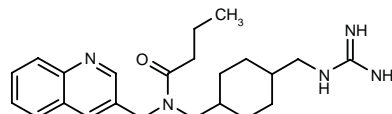
SOURCE – AstraZeneca.

REFERENCES

1. Delorme, D. et al. (Astra Pharma Inc.; Astra AB) *Novel cpds. useful in pain management.* WO 9967206.

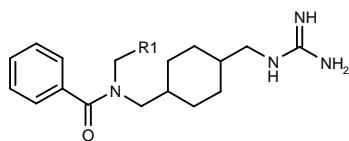
284763

N-[4-(Guanidinomethyl)cyclohexylmethyl]-N-(3-quinolin-ylmethyl)butyramide



C₂₃ H₃₃ N₅ O; Mol wt: 395.5477

ACTION – Agent for the treatment of pain, gastrointestinal disorders and spinal injuries, a selective δ-opioid receptor ligand. Other specifically claimed compounds within this series of 1,4-substituted cyclohexyl derivatives include the following:



Compound	R1	Isomer	Formula
284764	CH(Ph) ₂	cis	C ₃₀ H ₃₆ N ₄ O
284765	cyclohexyl	trans	C ₂₃ H ₃₆ N ₄ O

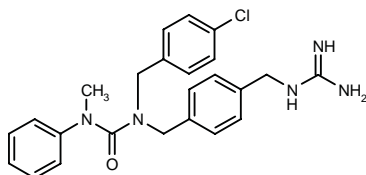
SOURCE – AstraZeneca.

REFERENCES

1. Delorme, D. et al. (Astra Pharma Inc.;Astra AB) *Novel cpds. useful in pain management*. WO 9967203.

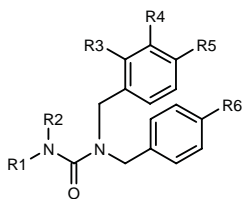
284788

N-(4-Chlorobenzyl)-*N*-[4-(guanidinomethyl)benzyl]-*N'*-methyl-*N'*-phenylurea

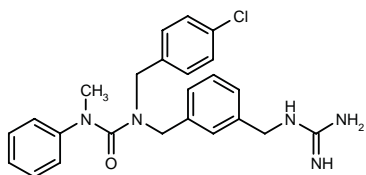


C₂₄ H₂₆ Cl N₅ O; Mol wt: 435.9564

ACTION – Agent for the treatment of pain, gastrointestinal disorders and spinal injuries, a selective δ -opioid receptor ligand. Other specifically claimed compounds within this series of 1,4-substituted phenyl derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
284789	Me	Me	H	H	Cl	CH ₂ NHC(=NH)NH ₂	C ₁₉ H ₂₄ ClN ₅ O
284790	H	3-NO ₂ -Ph	H	H	Cl	CH ₂ NHC(=NH)NH ₂	C ₂₃ H ₂₃ ClN ₅ O ₃
284791	H	4-PhO-Ph	H	H	Cl	CH ₂ NHC(=NH)NH ₂	C ₂₉ H ₂₈ ClN ₅ O ₂
284792	Me	Ph	Cl	H	H	CH ₂ NHC(=NH)NH ₂	C ₂₄ H ₂₆ ClN ₅ O
284793	Me	Ph	H	Cl	H	CH ₂ NHC(=NH)NH ₂	C ₂₄ H ₂₆ ClN ₅ O
284794	Me	Ph	H	H	H	CH ₂ NHC(=NH)NH ₂	C ₂₄ H ₂₇ N ₅ O
284795	Me	Ph	Cl	H	Cl	CH ₂ NHC(=NH)NH ₂	C ₂₄ H ₂₅ Cl ₂ N ₅ O
284796	Me	Ph	H	H	Cl	CH ₂ NH ₂	C ₂₃ H ₂₄ ClN ₃ O
284797	Me	Ph	H	H	Cl	1-pyrrolidinyl-CH ₂	C ₂₇ H ₃₀ ClN ₃ O
284798	Me	Ph	H	H	Cl	CH ₂ N(Me) ₂	C ₂₅ H ₂₈ ClN ₃ O
284799	Me	Ph	H	H	Cl	CH ₂ NHMe	C ₂₄ H ₂₆ ClN ₃ O



284810: C₂₄ H₂₆ Cl N₅ O

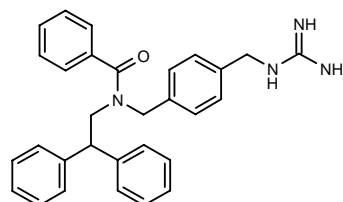
SOURCE – AstraZeneca.

REFERENCES

1. Delorme, D. et al. (Astra Pharma Inc.;Astra AB) *Novel cpds*. WO 9967204.

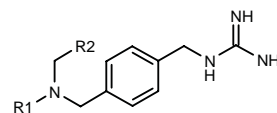
284800

N-[4-(Guanidinomethyl)benzyl]-*N*-(2,2-diphenylethyl)-benzamide

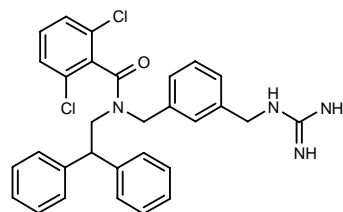


C₃₀ H₃₀ N₄ O; Mol wt: 462.5940

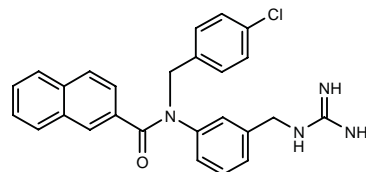
ACTION – Agent for the treatment of pain, gastrointestinal disorders and spinal injuries, a selective δ -opioid receptor ligand. Other specifically claimed compounds within this series of guanidinomethyl-substituted phenyl derivatives include the following:



Compound	R1	R2	Formula
284801	1-Naph-CO	4-Cl-Ph	C ₂₇ H ₂₅ ClN ₄ O
284802	2,6-(Cl) ₂ -PhCO	CH(Ph) ₂	C ₃₀ H ₂₈ Cl ₂ N ₄ O
284805	4-i-Pr-PhSO ₂	4-Cl-Ph	C ₂₅ H ₂₆ ClN ₄ O ₂ S
284806	COPh	3-Me-2-benzothienyl	C ₂₆ H ₂₆ N ₄ OS
284807	COPh	1-Naph	C ₂₇ H ₂₆ N ₄ O
284808	COPh	3-F-Ph	C ₂₃ H ₂₃ FN ₄ O



284803: C₃₀ H₂₈ Cl₂ N₄ O



284804: C₂₆ H₂₃ Cl N₄ O

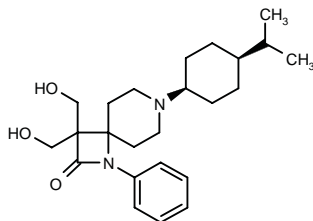
SOURCE – AstraZeneca.

REFERENCES

1. Delorme, D. et al. (Astra Pharma Inc.;Astra AB) *Novel cpds. useful in pain management*. WO 9967205.

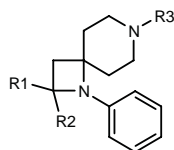
284894

cis-3,3-Bis(hydroxymethyl)-7-[4-(isopropyl)cyclohexyl]-1-phenyl-1,7-diazaspiro[3.5]nonan-2-one



C24 H36 N2 O3; Mol wt: 400.5594

ACTION – Orphanin FQ (OFQ, nociceptin, ORL1) receptor modulator with potential in the treatment of a broad range of diseases such as anxiety, stress disorders, depression, trauma, memory loss, epilepsy, pain, drug withdrawal symptoms, control of water balance and Na⁺ excretion, arterial blood pressure disorders and metabolic disorders such as obesity. Other specifically claimed compounds from this series of diazaspiro[3.5]nonane derivatives include the following:



Compound	R1	R2	R3	Formula
284896	-O-		cis-4-i-Pr-cyclohexyl	C ₂₂ H ₃₂ N ₂ O
284897	H	H	cis-4-i-Pr-cyclohexyl	C ₂₂ H ₃₄ N ₂
284899	-O-		cyclononyl	C ₂₂ H ₃₂ N ₂ O
284900	H	H	cyclononyl	C ₂₂ H ₃₄ N ₂
284901	-O-		cyclooctyl	C ₂₁ H ₃₀ N ₂ O
284903	-O-		cycloheptyl	C ₂₀ H ₂₈ N ₂ O
284904	-O-		(2 <i>r</i> ,4 <i>at</i> ,8 <i>at</i>)-decahydro-2-Naph	C ₂₃ H ₃₂ N ₂ O

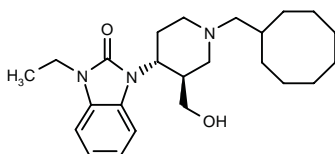
SOURCE – Roche.

REFERENCES

- Adam, G. et al. (F. Hoffmann-La Roche AG) *Diaza-spiro[3.5]nonane derivs.* CA 2274202, EP 0970957.

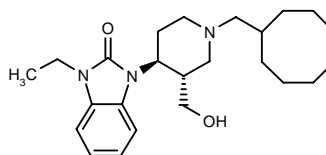
J-113397¹⁻³**282637**

1-[1-(Cyclooctylmethyl)-3(*R*)-(hydroxymethyl)piperidin-4(*R*)-yl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one



C24 H37 N3 O2; Mol wt: 399.5753

ACTION – Opioid receptor-like (ORL1, nociceptin, orphanin FQ) receptor antagonist (IC₅₀ = 2.3 nM against [¹²⁵I]-Tyr14-nociceptin binding in CHO cells expressing the human receptor) with high selectivity over μ-, γ- and δ-opioid receptors (IC₅₀ = 2200, 1400 and > 10,000 nM, respectively). The compound is under evaluation as an analgesic and for enhancing cognition. Its (3*S*,4*S*)-enantiomer **J-112444** was approximately 400-fold less active.



J-112444 [282638]^{1,2}: C24 H37 N3 O2

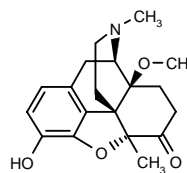
SOURCE – Banyu.

REFERENCES

- Ozaki, S. et al. (Banyu Pharmaceutical Co., Ltd.) *2-Oxoimidazole derivs.* WO 9854168.
- Kawamoto, H. et al. *Discovery of the first potent and selective small molecule opioid receptor-like (ORL1) antagonist: 1-[(3*R*,4*R*)-1-cyclooctylmethyl]-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one(J-113397).* J Med Chem 1999, 42(25): 5061.
- ORL1 antagonist J-113397 also being explored for cognition enhancement. DailyDrugNews.com (Daily Essentials) 2000, Feb 14.

14-METHOXYMETOPON**283383**

4,5α-Epoxy-3-hydroxy-14-methoxy-5,17-dimethylmorphinan-6-one



C19 H23 N O4; Mol wt: 329.3937

ACTION – Opiate analgesic agent, a potent and selective μ-opioid receptor agonist that is much more potent than morphine in the acetic acid-induced abdominal constriction test in mice and the hot-plate and tail-flick tests in rats, but which appears to be associated with less tolerance and dependence liability.

SOURCE – Universität Innsbruck, Innsbruck (AT).

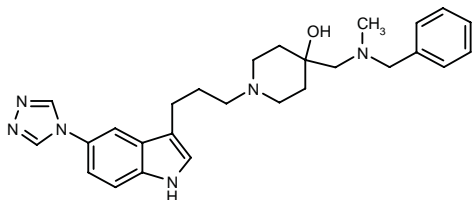
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ANTIMIGRAINE DRUGS

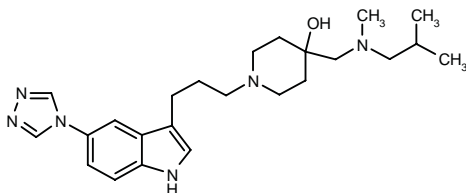
283985

3-[3-[4-(*N*-Benzyl-*N*-methylaminomethyl)-4-hydroxy-piperidin-1-yl]propyl]-5-(1,2,4-triazol-4-yl)-1*H*-indole



C₂₇ H₃₄ N₆ O; Mol wt: 458.6066

ACTION – 5-HT_{1D} receptor agonist with 80-fold selectivity over 5-HT_{1B} receptors (IC₅₀ = 1.2 and 96 nM, respectively, for displacement of [³H]-5-HT binding to cloned 5-HT_{1D} and 5-HT_{1B} receptors stably expressed in CHO cells). Compound showed full 5-HT_{1D}-agonist activity, as demonstrated by the ability to induce [³⁵S]-GTPγS binding in CHO cells (ED₅₀ = 3.8 nM). Potentially useful for the treatment of migraine. Another representative compound from this series of 1-(indol-3-yl-propyl)piperidines is:



283986: C₂₄ H₃₆ N₆ O

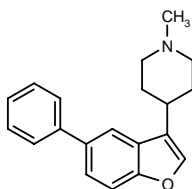
SOURCES – Merck & Co.

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2. Chen, C.-Y. and Larsen, R.D. (Merck & Co., Inc.) Palladium catalyzed indolization. US 5808064, WO 9806725.
3. Bourrain, S. et al. 4-Hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidines: Selective h5-HT_{1D} agonists for the treatment of migraine. Bioorg Med Chem Lett 1999, 9(23): 3369.

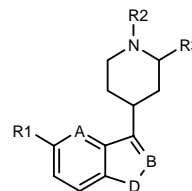
284718

1-Methyl-4-(5-phenylbenzofuran-3-yl)piperidine

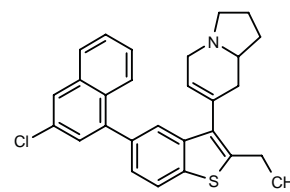


C₂₀ H₂₁ N O; Mol wt: 291.3919

ACTION – Agent for the treatment of migraine and associated disorders with 5-HT_{1F} receptor-agonist activity. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	B	D	Formula
284719	3-MeO-Ph	-(CH2)4-	CH	N	NH	C ₂₃ H ₂₇ N ₃	
284720	3-thienyl	i-Pr	H	CH	C(Bu)	S	C ₂₄ H ₃₁ NS ₂
284721	2-pyrazinyl	-(CH2)4-	N	C(t-Bu)	NH	C ₂₄ H ₃₁ N ₅	
284722	5-isothiazolyl	t-Bu	H	CH	CH	NH	C ₂₀ H ₂₅ N ₃ S
284723	2-benzimidazolyl	-(CH2)4-	CH	CH	O	C ₂₄ H ₂₅ N ₃ O	
284724	2-Naph	Me	H	CH	N	NH	C ₂₃ H ₂₃ N ₃
284726	2-(CONH2)-1-Naph	Pr	H	N	C(cyclopropyl)	NH	C ₂₉ H ₃₂ N ₄ O



284725: C₂₈ H₂₆ Cl N S

SOURCE – Lilly.

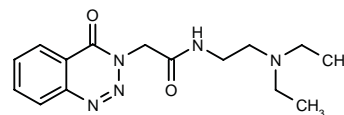
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1. Koch, D.J. et al. (Eli Lilly and Company) 5-HT_{1F} agonists. WO 0000487.

ANESTHETIC DRUGS

284663

N-[2-(Diethylamino)ethyl]-2-(4-oxo-1,2,3-benzotriazin-3-yl)acetamide



C₁₅ H₂₁ N₅ O₂; Mol wt: 303.3639

M.p. 155-6 °C.

ACTION – Local anesthetic with activity comparable to that of lidocaine in the mouse tail-pinch test (IC₅₀ = 6.9 and 6.8 mM for compound and lidocaine, respectively) and somewhat less active as an anesthetic in rabbit cornea (69% of the anesthetic activity of lidocaine [= 100%]). Compound given as a 2% solution (0.2 ml) on the posterior side of the femur head exhibited better activity than lidocaine in blocking rat sciatic nerve conduction; in fact, it induced long-lasting motor paralysis (160 min) compared to lidocaine (117 min). In rat isolated right atria, only high concentrations (> 100 μM) induced a negative chronotropic effect. It showed a slightly higher therapeutic index than lidocaine (LD₅₀/IC₅₀ in the mouse tail test = 8.83 vs. 8.23).

SOURCE – Università degli Studi di Napoli, Napoli (IT).

REFERENCES

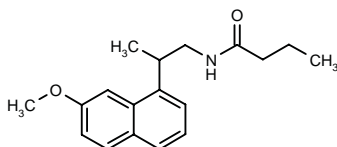
1. Callendo, G. et al. *Preparation and local anaesthetic activity of benzotriazinone and benzoyltriazole derivatives*. Eur J Med Chem 1999, 34(12): 1043.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

284685

(±)-N-[2-(7-Methoxynaphthalen-1-yl)propyl]butyramide



C18 H23 N O2; Mol wt: 285.3847

ACTION – High-affinity melatonin receptor ligand ($K_i = 0.032$ nM for displacement of 2-[¹²⁵I]-iodomelatonin from chicken brain melatonin receptors) with full agonist activity, as demonstrated by its ability to produce lightening of the skin of *Xenopus laevis*. In comparison to melatonin, compound showed 20-fold higher affinity for melatonin receptors and 25-fold greater agonist activity in the *X. laevis* assay. Potentially useful for circadian rhythm disorders.

SOURCE – CNRS.

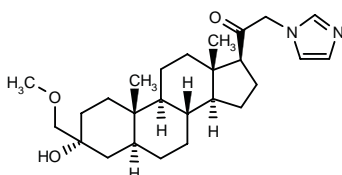
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1. Mathé-Allainmat, M. et al. *Synthesis of β-substituted naphth-1-yl ethylamido derivatives as new melatonergic agonists*. Bioorg Med Chem 1999, 7(12): 2945.

CO-134444³

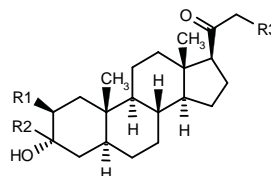
284014

3α-Hydroxy-21-(1-imidazolyl)-3-(methoxymethyl)-5α-pregnan-20-one



C26 H40 N2 O3; Mol wt: 428.6130

ACTION – Orally active neuroactive steroid proven to induce a dose-dependent suppression of response rates in an operant lever-pressing task in rats ($SD_{50} = 10.4$ mg/kg p.o.) and dose-dependent increases in ataxia ($TD_{50} = 28.3$ mg/kg p.o.). Compound also induced significant increases in NREM sleep at doses having no effect on REM sleep (minimum significant dose [MSD] = 12 mg/kg p.o.). Together with its good oral bioavailability, rapid onset of effect and solubility in aqueous media, this profile suggests potential as a sedative/hypnotic. Other neuroactive steroids include the following:



Compound	R1	R2	R3	Formula
Co-177843 [284015] ³	H	CH2OMe	1-oxido-6-quinolyl-O	C ₃₂ H ₄₃ NO ₅
Co-127501 [284016] ¹⁻³	ethynyl	H	H	C ₂₃ H ₃₄ O ₂

SOURCE – CoCensys.

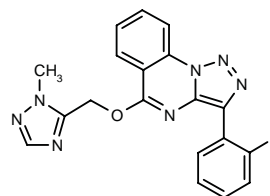
REFERENCES

1. Lan, N.C. (CoCensys, Inc.) *Use of GABA and NMDA receptor ligands for the treatment of migraine headache*. WO 9805337.
2. Upasani, R.B. et al. (CoCensys, Inc.) *Androstanes and pregnanes for allosteric modulation of GABA receptor*. EP 0752860, JP 1997510701, WO 9521617.
3. Vanover, K.E. et al. *Response-rate suppression in operant paradigm as predictor of soporific potency in rats and identification of three novel sedative-hypnotic neuroactive steroids*. J Pharmacol Exp Ther 1999, 291(3): 1317.

ANXIOLYTICS

284538

3-(2-Fluorophenyl)-5-(1-methyl-1H-1,2,4-triazol-5-yl-methoxy)[1,2,3]triazolo[1,5-a]quinazoline



C19 H14 F N7 O; Mol wt: 375.3656

ACTION – Anxiolytic agent and anticonvulsant with selective affinity for the α_2 and/or α_3 subunits of the human GABA_A receptor relative to the α_1 subunit; compound is reported to have K_i values for displacement of [³H]-flumazenil from the α_2 and/or α_3 subunit of the human GABA_A receptor of 100 nM or less. Other specifically claimed compounds from this series of [1,2,3]triazolo[1,5-a]pyrimidine derivatives include the following:

SOURCE – Università degli Studi di Napoli, Napoli (IT).

REFERENCES

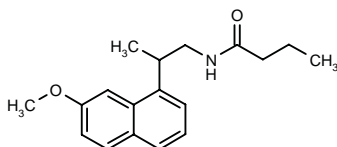
1. Callendo, G. et al. *Preparation and local anaesthetic activity of benzotriazinone and benzoyltriazole derivatives*. Eur J Med Chem 1999, 34(12): 1043.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

284685

(±)-N-[2-(7-Methoxynaphthalen-1-yl)propyl]butyramide



C18 H23 N O2; Mol wt: 285.3847

ACTION – High-affinity melatonin receptor ligand ($K_i = 0.032$ nM for displacement of 2-[125 I]-iodomelatonin from chicken brain melatonin receptors) with full agonist activity, as demonstrated by its ability to produce lightening of the skin of *Xenopus laevis*. In comparison to melatonin, compound showed 20-fold higher affinity for melatonin receptors and 25-fold greater agonist activity in the *X. laevis* assay. Potentially useful for circadian rhythm disorders.

SOURCE – CNRS.

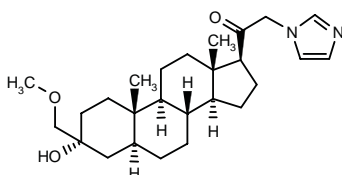
REFERENCES

1. Mathé-Allainmat, M. et al. *Synthesis of β -substituted naphth-1-yl ethylamido derivatives as new melatonergic agonists*. Bioorg Med Chem 1999, 7(12): 2945.

CO-134444³

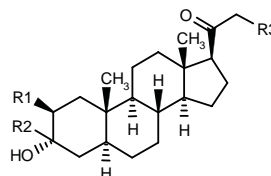
284014

3 α -Hydroxy-21-(1-imidazolyl)-3-(methoxymethyl)-5 α -pregnan-20-one



C26 H40 N2 O3; Mol wt: 428.6130

ACTION – Orally active neuroactive steroid proven to induce a dose-dependent suppression of response rates in an operant lever-pressing task in rats ($SD_{50} = 10.4$ mg/kg p.o.) and dose-dependent increases in ataxia ($TD_{50} = 28.3$ mg/kg p.o.). Compound also induced significant increases in NREM sleep at doses having no effect on REM sleep (minimum significant dose [MSD] = 12 mg/kg p.o.). Together with its good oral bioavailability, rapid onset of effect and solubility in aqueous media, this profile suggests potential as a sedative/hypnotic. Other neuroactive steroids include the following:



Compound	R1	R2	R3	Formula
Co-177843 [284015] ³	H	CH2OMe	1-oxido-6-quinolyl-O	C ₃₂ H ₄₃ NO ₅
Co-127501 [284016] ¹⁻³	ethynyl	H	H	C ₂₃ H ₃₄ O ₂

SOURCE – CoCensys.

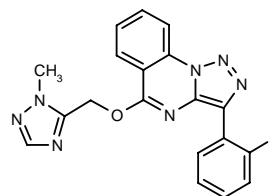
REFERENCES

1. Lan, N.C. (CoCensys, Inc.) *Use of GABA and NMDA receptor ligands for the treatment of migraine headache*. WO 9805337.
2. Upasani, R.B. et al. (CoCensys, Inc.) *Androstanes and pregnanes for allosteric modulation of GABA receptor*. EP 0752860, JP 1997510701, WO 9521617.
3. Vanover, K.E. et al. *Response-rate suppression in operant paradigm as predictor of soporific potency in rats and identification of three novel sedative-hypnotic neuroactive steroids*. J Pharmacol Exp Ther 1999, 291(3): 1317.

ANXIOLYTICS

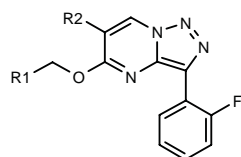
284538

3-(2-Fluorophenyl)-5-(1-methyl-1H-1,2,4-triazol-5-yl-methoxy)[1,2,3]triazolo[1,5-a]quinazoline



C19 H14 F N7 O; Mol wt: 375.3656

ACTION – Anxiolytic agent and anticonvulsant with selective affinity for the α_2 and/or α_3 subunits of the human GABA_A receptor relative to the α_1 subunit; compound is reported to have K_i values for displacement of [3 H]-flumazenil from the α_2 and/or α_3 subunit of the human GABA_A receptor of 100 nM or less. Other specifically claimed compounds from this series of [1,2,3]triazolo[1,5-a]pyrimidine derivatives include the following:



Compound	R1	R2	Formula
284539	1-Me-1,2,4-triazol-5-yl	Ph	C ₂₁ H ₁₆ FN ₇ O
284541	1-Me-1,2,4-triazol-5-yl	cyclobutyl	C ₁₉ H ₁₆ FN ₇ O
284542	1-Me-1,2,4-triazol-3-yl	cyclobutyl	C ₁₉ H ₁₆ FN ₇ O
284543	1-Et-1H-1,2,4-triazol-5-yl	cyclobutyl	C ₂₀ H ₂₀ FN ₇ O
284544	1-Me-1,2,4-triazol-3-yl	Ph	C ₂₁ H ₁₆ FN ₇ O
284545	1-Et-1H-1,2,4-triazol-5-yl	Ph	C ₂₂ H ₁₈ FN ₇ O

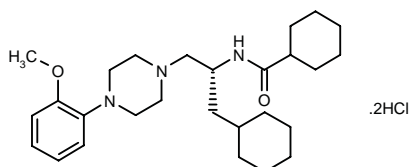
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Broughton, H.B. et al. (Merck Sharp & Dohme Ltd.) *Triazolo-pyrimidines as ligands for GABA receptors*. WO 9965907.

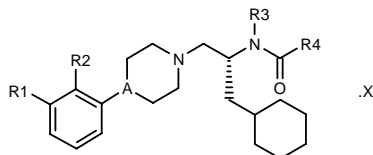
284571

N-[2-Cyclohexyl-1(*R*)-[4-(2-methoxyphenyl)piperazin-1-ylmethyl]ethyl]cyclohexanecarboxamide dihydrochloride



C₂₇ H₄₃ N₃ O₂ · 2HCl; Mol wt: 514.5775

ACTION – Agent for the treatment of anxiety, depression, schizophrenia, cognitive deficits resulting from neurodegenerative disorders such as Alzheimer's disease, nausea and vomiting, and prostate cancer, a selective 5-HT_{1A} receptor partial agonist. Compound exhibited an IC₅₀ value of 0.57 nM for displacement of [³H]-8-OH-DPAT binding in CHO cells stably transfected with the human receptor; partial agonist activity was demonstrated by its ability to stimulate the binding of [³⁵S]-GTPγS in these cells with an EC₅₀ of 0.9 nM. A representative compound from a series of cycloalkyl-substituted aryl-piperazines, piperidines and tetrahydropyridines, wherein the following are also included:



Compound	R1	R2	R3	R4	A	X	Formula
284572	H	OMe	H	1-Me-cyclohexyl	N	HCl H ₂ O	C ₂₈ H ₄₅ N ₃ O ₂ .HCl.H ₂ O
284574	H	OMe	Me	cyclohexyl	N	2HCl	C ₂₈ H ₄₅ N ₃ O ₂ .2HCl
284575	H	OMe	Me	1-Me-cyclohexyl	N	2HCl	C ₂₉ H ₄₇ N ₃ O ₂ .2HCl
284576	-OCH ₂ CH ₂ O-	Me	cyclohexyl	N	HCl H ₂ O		C ₂₉ H ₄₅ N ₃ O ₃ .HCl.H ₂ O

Compound	R1	R2	R3	R4	A	X	Formula
284577	-OCH ₂ CH ₂ O-	Me	Me	1-Me-cyclohexyl	N	HCl	C ₃₀ H ₄₇ N ₃ O ₃ .HCl
284579	-NHCH=CH-	Me	Me	cyclohexyl	N	HCl H ₂ O	C ₂₉ H ₄₄ N ₄ O .HCl.H ₂ O
284581	H	OMe	H	H	N	HCl H ₂ O	C ₂₁ H ₃₃ N ₃ O ₂ .HCl.H ₂ O
284582	H	OMe	H	cyclohexyl	CH	HCl H ₂ O	C ₂₈ H ₄₄ N ₂ O ₂ .HCl.H ₂ O

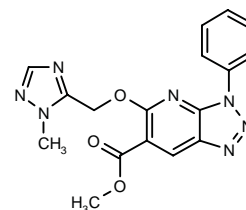
SOURCE – American Home Products.

REFERENCES

1. Childers, W.E. et al. (American Home Products Corp.) *Cycloalkyl-substd. aryl-piperazines, piperidines and tetrahydropyridines as serotonergic agents*. WO 9965887.

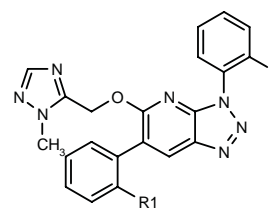
284628

5-(1-Methyl-1*H*-1,2,4-triazol-5-ylmethoxy)-3-phenyl-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine-6-carboxylic acid methyl ester



C₁₇ H₁₅ N₇ O₃; Mol wt: 365.3515

ACTION – Anxiolytic agent and anticonvulsant with selective affinity for the α₂ and/or α₃ subunits of the human GABA_A receptor relative to the α₁ subunit; compound is reported to have K_i values for displacement of [³H]-flumazenil from the α₂ and/or α₃ subunit of the human GABA_A receptor of 100 nM or less. Other specifically claimed compounds from this series of [1,2,3]triazolo[4,5-*b*]pyridine derivatives include the following:



Compound	R1	Formula
284629	H	C ₂₁ H ₁₆ FN ₇ O
284631	F	C ₂₁ H ₁₅ F ₂ N ₇ O

SOURCE – Merck Sharp & Dohme.

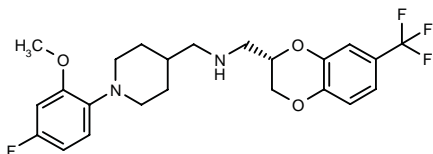
REFERENCES

1. Broughton, H.B. et al. (Merck Sharp & Dohme Ltd.) *Triazolo-pyridine derivs. as ligands for GABA receptors*. WO 9965904.

ANTIPSYCHOTIC DRUGS

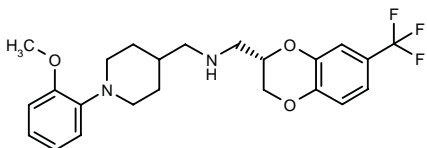
284154

N-[1-(4-Fluoro-2-methoxyphenyl)piperidin-4-ylmethyl]-*N*-[7-(trifluoromethyl)-2,3-dihydro-1,4-benzodioxin-2(*S*)-ylmethyl]amine



C23 H26 F4 N2 O3; Mol wt: 454.4614

ACTION – Agent for the treatment of CNS disorders such as depression, anxiety, psychoses, tardive dyskinesia, Parkinson's disease, Tourette's syndrome, sexual dysfunction, drug addiction, Alzheimer's disease, panic attacks and eating disorders, as well as obesity, cardiovascular and cerebrovascular disorders and diabetes, with potent affinity for 5-HT_{1A} and dopamine D₂ receptors (K_i = 23 and 65 nM, respectively) and lower affinity for α_1 -adrenoceptors (K_i = 183 nM). Antipsychotic efficacy was demonstrated by inhibition of apomorphine-induced climbing in mice with an ED₅₀ value of 1 mg/kg p.o. Another specifically claimed compound from this series of *N*-benzodioxanylmethyl-1-piperidyl-methylamine derivatives is:



284156: C23 H27 F3 N2 O3

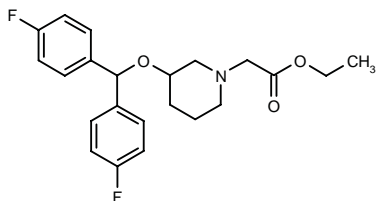
SOURCE – Knoll.

REFERENCES

1. Wishart, N. and Birch, A.M. (Knoll AG) *N*-Benzodioxanylmethyl-1-piperidyl-methylamine cpds. having affinity for 5-HT receptors. WO 9962902.

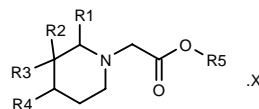
284188

2-[3-[Bis(4-fluorophenyl)methoxy]piperidin-1-yl]acetic acid ethyl ester



C22 H25 F2 N O3; Mol wt: 389.4395

ACTION – An inhibitor of glycine transport via the GlyT-1 or GlyT-2 transporter, potentially useful for the treatment or prevention of neurological and neuropsychiatric disorders such as schizophrenia, dementia, epilepsy, spasticity, muscle spasm, pain, depression, memory or learning disorders and for the prevention of neuronal cell death after stroke or in patients suffering from neurodegenerative diseases. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
284189	H	CH(Ph)2	bond		Et		C ₂₂ H ₂₅ NO ₂
284190	H	CH(Ph)2	H	H	Et		C ₂₂ H ₂₇ NO ₂
284191	CH ₂ CH(cyclohexyl)2	H	H	H	H	HCl	C ₂₃ H ₄₁ NO ₂ ·HCl

Agents that inhibit GlyT-1 and thereby increase glycine activation of NMDA receptors may be useful as antipsychotic and antimentia agents, and inhibitors of GlyT-2 can be used to reduce the activity of neurons with strychnine-sensitive glycine receptors by increasing synaptic levels of glycine, and are thus useful for reducing the transmission of pain-related information.

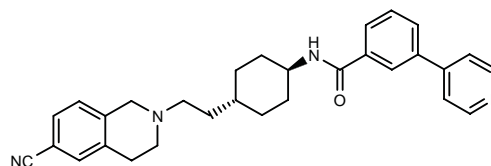
SOURCE – NPS Pharmaceuticals.

REFERENCES

1. Ognyanov, V.I. et al. (NPS Pharmaceuticals, Inc.) *Pharmaceutical for treating of neurological and neuropsychiatric disorders*. US 6001854.

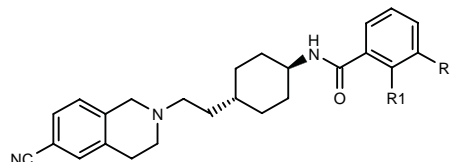
284309

trans-*N*-[4-[2-(6-Cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-3-(4-pyridyl)benzamide



C30 H32 N4 O; Mol wt: 464.6098

ACTION – Antipsychotic agent with selective affinity for dopamine D₃ receptors, a representative compound from a series of tetrahydroisoquinoline derivatives, wherein the following are also specifically claimed:



Compound	R1	R2	Formula
284310	H	3-Pyr	C ₃₀ H ₃₂ N ₄ O
284311	H	5-pyrimidinyl	C ₂₉ H ₃₁ N ₅ O
284312	H	2-furyl	C ₂₉ H ₃₁ N ₃ O ₂
284313	H	Ph	C ₃₁ H ₃₃ N ₃ O
284314	Ph	H	C ₃₁ H ₃₃ N ₃ O
284315	H	2-Me-4-Pyr	C ₃₁ H ₃₄ N ₄ O

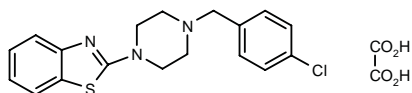
SOURCE – SmithKline Beecham.

REFERENCES

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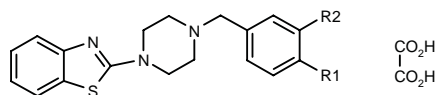
284707

2-[4-(4-Chlorobenzyl)piperazin-1-yl]benzothiazole oxalate



C₁₈H₁₈ClN₃S · C₂H₂O₄; Mol wt: 433.9140

ACTION – Agent for the treatment or prevention of CNS disorders including schizophrenia, mania, depression, anxiety, dementia, Parkinson's disease, tardive dyskinesias, drug abuse, obsessive-compulsive disorder and motor disorders associated with the use of neuroleptic agents, a highly potent and selective dopamine D₄ receptor antagonist ($K_i = 14$ nM) with markedly lower affinity for D₂ receptors ($K_i > 4000$ nM). Other compounds from this series of 1-(benzothiazol-2-yl)-4-(1-phenylmethyl)piperazines include the following:



Compound	R1	R2	Formula
284709	Me	H	C ₁₉ H ₂₁ N ₃ S · C ₂ H ₂ O ₄
284710	-CH=CHCH=CH-		C ₂₂ H ₂₁ N ₃ S · C ₂ H ₂ O ₄

SOURCE – Neurogen.

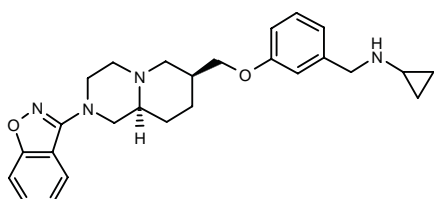
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TREATMENT FOR MOOD DISORDERS

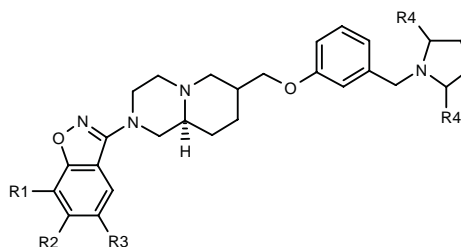
282272

trans-N-[3-[(7*S*,9*aS*)-2-(1,2-Benzisoxazol-3-yl)perhydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]benzyl]-*N*-cyclopropyl-amine

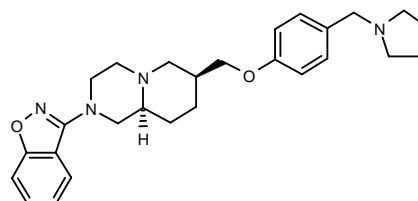


C₂₆H₃₂N₄O₂; Mol wt: 432.5648

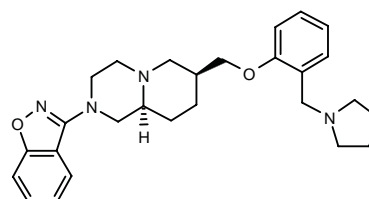
ACTION – Agent for the treatment of a broad range of disorders including depression, hypertension, anxiety, eating disorders, chemical dependence and migraine with affinity for 5-HT_{1A} and/or 5-HT_{1D} receptors. Other azabicyclic compounds include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
282273	H	H	F	H	7R	C ₂₇ H ₃₃ FN ₄ O ₂
282274	H	H	H	H	7S	C ₂₇ H ₃₄ N ₄ O ₂
282277	H	H	H	Me	7S	C ₂₉ H ₃₈ N ₄ O ₂
282279	F	F	H	H	7R	C ₂₇ H ₃₂ F ₂ N ₄ O ₂



282275: C₂₇ H₃₄ N₄ O₂



282278: C₂₇ H₃₄ N₄ O₂

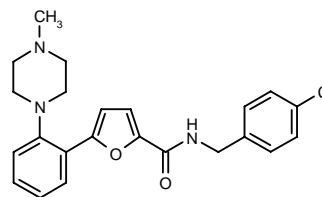
SOURCE – Pfizer.

REFERENCES

1. Bright, G.M. (Pfizer Products Inc.) *Azabicyclic 5HT₁ receptor ligands*. WO 9952907.

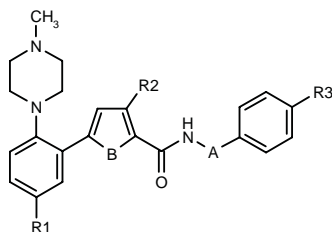
282949

N-(4-Chlorobenzyl)-5-[2-(4-methylpiperazin-1-yl)phenyl]-furan-2-carboxamide

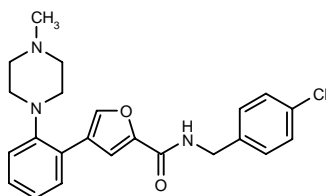


C₂₃H₂₄ClN₃O₂; Mol wt: 409.9146

ACTION – Psychotherapeutic agent from a series of potent agonists and/or antagonists of 5-HT_{1A} and/or 5-HT_{1D} receptors (IC₅₀ < 0.60 µM for 5-HT_{1D} and < 1.0 µM for 5-HT_{1A} receptors), potentially useful for the treatment of a broad range of disorders such as depression, anxiety, obsessive-compulsive and panic disorders, premature ejaculation, hypertension, eating disorders, migraine, Alzheimer's disease and Parkinson's disease. Other specifically claimed compounds from this series of heterocyclic carboxamides include the following:



Compound	R1	R2	R3	A	B	Formula
282950	H	H	Cl	bond	O	C ₂₂ H ₂₂ ClN ₃ O ₂
282951	H	H	Cl	bond	S	C ₂₂ H ₂₂ ClN ₃ OS
282952	H	H	Cl	-CH2-	S	C ₂₃ H ₂₄ ClN ₃ OS
282953	H	H	Cl	-(CH2)2-	O	C ₂₄ H ₂₆ ClN ₃ O ₂
282955	H	H	H	-CH2-	S	C ₂₃ H ₂₅ N ₃ OS
282956	H	H	F	-CH2-	S	C ₂₃ H ₂₄ FN ₃ OS
282957	H	H	OMe	-CH2-	S	C ₂₄ H ₂₇ N ₃ O ₂ S
282958	H	H	Cl	-(CH2)2-	S	C ₂₄ H ₂₆ ClN ₃ OS
282959	H	Me	Cl	-CH2-	S	C ₂₄ H ₂₆ ClN ₃ OS
282960	F	H	Cl	-CH2-	S	C ₂₃ H ₂₃ ClFN ₃ OS
282961	H	H	Cl	-CH2-	NH	C ₂₃ H ₂₅ ClN ₄ O



282954: C₂₃ H₂₄ Cl N₃ O₂

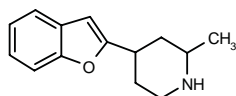
SOURCE – Pfizer.

REFERENCES

1. Howard, H.R. (Pfizer Products Inc.) *Heterocyclic carboxamides*. EP 0957099, JP 1999322711.

284759

4-(2-Benzofuryl)-2-methylpiperidine



C₁₄ H₁₇ N O; Mol wt: 215.2943

ACTION – Agent for the treatment of depression, obsessive-compulsive disorder and obesity, a representative compound from a series of 4-arylpiperidines with 5-HT reuptake-inhibitory activity.

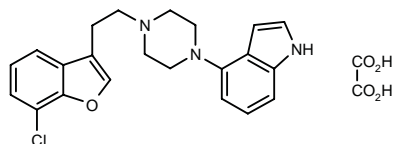
SOURCE – Lilly.

REFERENCES

1. Koch, D.J. and Rocco, V.P. (Eli Lilly and Company) *Inhibitors of serotonin reuptake*. EP 0965587, WO 9965487.

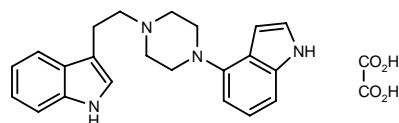
284824

4-[4-[2-(7-Chloro-1-benzofuran-3-yl)ethyl]piperazin-1-yl]-1H-indole hemioxalate

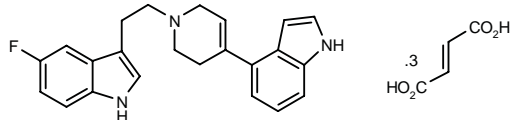


C₂₂ H₂₂ Cl N₃ O . C₂ H₂ O₄; Mol wt: 469.9226

ACTION – Agent for the treatment of CNS disorders, particularly depression, psychosis and anxiety, a dual 5-HT_{1A} receptor antagonist (IC₅₀ = 4.3 nM against [³H]-5-CT binding to cloned human 5-HT_{1A} receptors stably expressed in transfected HeLa cells) and 5-HT reuptake inhibitor (IC₅₀ = 4.4 nM in rat brain synaptosomes). Other compounds from this series of 4-, 5-, 6- and 7-indole and indoline derivatives include the following:



284825: C₂₂ H₂₄ N₄ . C₂ H₂ O₄



284826: C₂₃ H₂₂ F N₃ . 3 C₄ H₄ O₄

SOURCE – Lundbeck.

REFERENCES

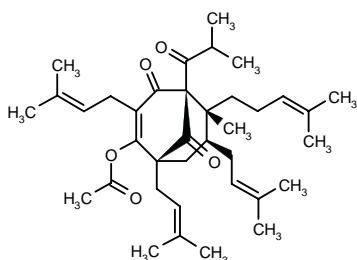
1. Moltzen, E.K. et al. (H. Lundbeck A/S) *4,5,6 and 7-indole and indoline derivs., their preparation and use*. WO 9967237.

HYPERFORIN ACETATE

284428

Acetic acid (1*S*,5*R*,6*R*,7*S*)-5-isobutyryl-6-methyl-1,3,7-tris(3-methyl-2-butenyl)-6-(4-methyl-3-pentenyl)-4,9-dioxobicyclo[3.3.1]non-2-en-2-yl ester

(1*S*,5*R*,6*R*,7*S*)-2-Acetoxy-5-isobutyryl-6-methyl-1,3,7-tris(3-methyl-2-butenyl)-6-(4-methyl-3-pentenyl)-bicyclo[3.3.1]non-2-ene-4,9-dione



C37 H54 O5; Mol wt: 578.8286

ACTION – Agent for the treatment of depression and anxiety, a derivative of hyperforin with improved chemical stability and superior antidepressant activity, as demonstrated in a rat paradigm. In addition, compound was also shown to reduce alcohol consumption in rats.

SOURCE – Indena.

REFERENCES

1. Bombardelli, E. and Marazzoni, P. (Indena SpA) *Hyperforin derivs., the use thereof and formulations containing them*. WO 9964388.

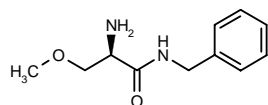
NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

283917^{1,2}

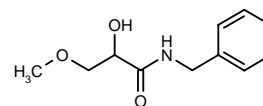
2(*R*)-Amino-*N*-benzyl-3-methoxypropionamide

*N*¹-Benzyl-*O*-methyl-D-serinamide



C11 H16 N2 O2; Mol wt: 208.2594

ACTION – Anticonvulsant proven to inhibit maximal electroshock-induced seizures in rats with an ED₅₀ of 18 mg/kg p.o., without inducing ataxia (TD₅₀ = 500 mg/kg p.o. in the rotarod test in rats). A related *N*-benzyl 3-methoxypropionamide is:



283916²: C11 H15 N O3

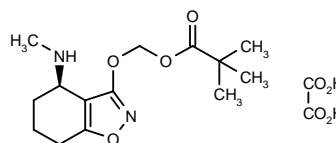
SOURCES – University of Houston, Houston, TX (US); National Institutes of Health, Bethesda, MD (US); Research Corporation Technologies.

REFERENCES

1. Kohn, H. and Andurkar, S.V. (Research Corporation Technologies, Inc.) *Anticonvulsant enantiomeric amino acid derivs*. WO 0000463.
2. Andurkar, S.V. et al. *The anticonvulsant activities of N-benzyl 3-methoxypropionamides*. Bioorg Med Chem 1999, 7(11): 2381.

284106

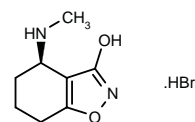
Pivalic acid (+)-4(*R*)-(methylamino)-4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yloxymethyl ester hemioxalate



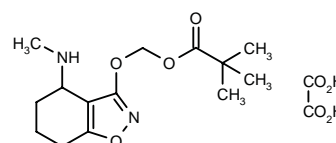
C14 H22 N2 O4 . C2 H2 O4; Mol wt: 372.3716

M.p. 210-3 °C; $[\alpha]_D^{25} +5.6^\circ$ (*c* 1.0, MeOH).

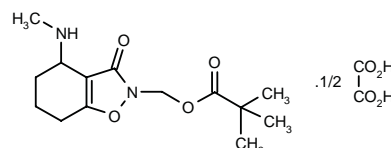
ACTION – Anticonvulsant, a lipophilic pivaloyloxymethyl prodrug of **284104** proven to protect against isoniazid-induced seizures in mice following s.c. administration (ED₅₀ = 44 μmol/kg), whereas the active compound was inactive after this route of administration; however, the latter was effective against audiogenic seizures in mice following intracerebroventricular administration (ED₅₀ = 59 nmol). The active compound acts as a selective glial GABA uptake inhibitor, with IC₅₀ values of 60, 39 and 510 μM for inhibition of GABA uptake in astrocytes, synaptosomes and cortical neurons, respectively. The *O*- and *N*-pivaloyloxymethyl derivatives of racemic active compound are also described:



284104: C8 H12 N2 O2 . HBr



284105: C14 H22 N2 O4 . C2 H2 O4



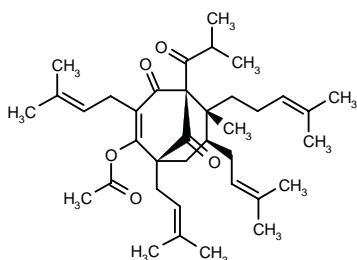
284107: C14 H22 N2 O4 . 1/2 C2 H2 O4

HYPERFORIN ACETATE

284428

Acetic acid (1*S*,5*R*,6*R*,7*S*)-5-isobutyryl-6-methyl-1,3,7-tris(3-methyl-2-butenyl)-6-(4-methyl-3-pentenyl)-4,9-dioxobicyclo[3.3.1]non-2-en-2-yl ester

(1*S*,5*R*,6*R*,7*S*)-2-Acetoxy-5-isobutyryl-6-methyl-1,3,7-tris(3-methyl-2-butenyl)-6-(4-methyl-3-pentenyl)-bicyclo[3.3.1]non-2-ene-4,9-dione



C37 H54 O5; Mol wt: 578.8286

ACTION – Agent for the treatment of depression and anxiety, a derivative of hyperforin with improved chemical stability and superior antidepressant activity, as demonstrated in a rat paradigm. In addition, compound was also shown to reduce alcohol consumption in rats.

SOURCE – Indena.

REFERENCES

1. Bombardelli, E. and Marazzoni, P. (Indena SpA) *Hyperforin derivs., the use thereof and formulations containing them*. WO 9964388.

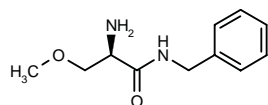
NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

283917^{1,2}

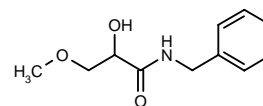
2(*R*)-Amino-*N*-benzyl-3-methoxypropionamide

*N*¹-Benzyl-*O*-methyl-D-serinamide



C11 H16 N2 O2; Mol wt: 208.2594

ACTION – Anticonvulsant proven to inhibit maximal electroshock-induced seizures in rats with an ED₅₀ of 18 mg/kg p.o., without inducing ataxia (TD₅₀ = 500 mg/kg p.o. in the rotarod test in rats). A related *N*-benzyl 3-methoxypropionamide is:



283916²: C11 H15 N O3

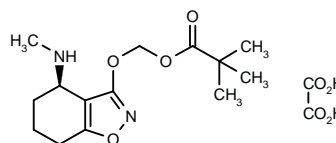
SOURCES – University of Houston, Houston, TX (US); National Institutes of Health, Bethesda, MD (US); Research Corporation Technologies.

REFERENCES

1. Kohn, H. and Andurkar, S.V. (Research Corporation Technologies, Inc.) *Anticonvulsant enantiomeric amino acid derivs*. WO 0000463.
2. Andurkar, S.V. et al. *The anticonvulsant activities of N-benzyl 3-methoxypropionamides*. Bioorg Med Chem 1999, 7(11): 2381.

284106

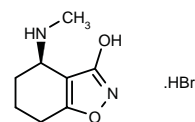
Pivalic acid (+)-4(*R*)-(methylamino)-4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yloxymethyl ester hemioxalate



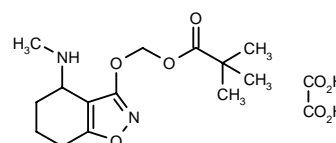
C14 H22 N2 O4 . C2 H2 O4; Mol wt: 372.3716

M.p. 210-3 °C; $[\alpha]_D^{25} +5.6^\circ$ (*c* 1.0, MeOH).

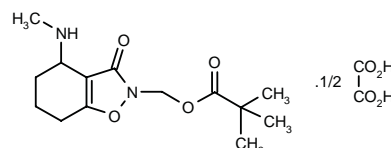
ACTION – Anticonvulsant, a lipophilic pivaloyloxymethyl prodrug of **284104** proven to protect against isoniazid-induced seizures in mice following s.c. administration (ED₅₀ = 44 μmol/kg), whereas the active compound was inactive after this route of administration; however, the latter was effective against audiogenic seizures in mice following intracerebroventricular administration (ED₅₀ = 59 nmol). The active compound acts as a selective glial GABA uptake inhibitor, with IC₅₀ values of 60, 39 and 510 μM for inhibition of GABA uptake in astrocytes, synaptosomes and cortical neurons, respectively. The *O*- and *N*-pivaloyloxymethyl derivatives of racemic active compound are also described:



284104: C8 H12 N2 O2 . HBr



284105: C14 H22 N2 O4 . C2 H2 O4



284107: C14 H22 N2 O4 . 1/2 C2 H2 O4

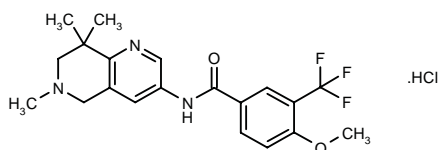
SOURCE – Lundbeck.

REFERENCES

1. Falch, E. et al. (H. Lundbeck A/S) 4-Aminotetrahydrobenzoxazole or -isothiazole cpds. WO 9626929.
2. Falch, E. et al. *Selective inhibitors of glial GABA uptake: Synthesis, absolute stereochemistry, and pharmacology of the enantiomers of 3-hydroxy-4-amino-4,5,6,7-tetrahydro-1,2-benzisoxazole (exo-THPO) and analogues.* J Med Chem 1999, 42(26): 5402.

284469

4-Methoxy-3-(trifluoromethyl)-N-(6,8,8-trimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)benzamide hydrochloride



C20 H22 F3 N3 O2 . HCl; Mol wt: 429.8677

ACTION – Anticonvulsant that binds to the receptor site in rat brain labeled by [³H]-SB-204269 with a pK_i value > 8. The compound elevated the threshold for electrically induced seizures in the maximal electroshock seizure threshold test in rats by 314% at a dose of 2 mg/kg p.o. Potentially useful in the treatment of epilepsy, anxiety, depression, withdrawal from substances of abuse, Parkinson's disease, psychosis, migraine, cerebral ischemia, Alzheimer's disease, sleep disorders, neuropathic pain, multiple sclerosis, amyotrophic lateral sclerosis, etc. Another exemplified tetrahydronaphthyridinyl-carboxamide is:



284470: C20 H24 Br N3 O2 . HCl

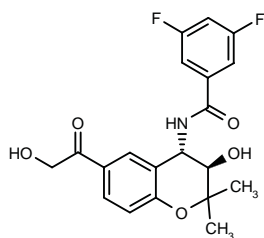
SOURCE – SmithKline Beecham.

REFERENCES

1. Harling, J.D. et al. (SmithKline Beecham plc) *Tetrahydronaphthyridinyl-carboxamides having anti-convulsant activity.* WO 9965903.

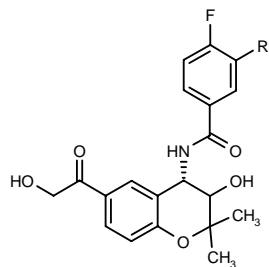
284699

3,5-Difluoro-N-[3(R)-hydroxy-6-(2-hydroxyacetyl)-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4(S)-yl]-benzamide



C20 H19 F2 N O5; Mol wt: 391.3681

ACTION – Anticonvulsant that binds to the site labeled by [³H]-SB-204269, displaying a pK_i value of 7.35 in a binding assay using rat forebrain homogenates. It was effective in elevating the seizure threshold in the maximal electroshock seizure test in rats, with an increase of 317% relative to control at a dose of 1 mg/kg i.v. Potentially useful in the treatment and/or prophylaxis of epilepsy, as well as anxiety, depression, withdrawal from substances of abuse, Parkinson's disease, schizophrenia, cerebral ischemia, migraine, Alzheimer's disease, etc. Other specifically claimed substituted benzopyran derivatives are:



Compound	R1	Isomer	Formula
284700	Cl	S	C ₂₀ H ₁₉ ClFNO ₅
284701	H	R	C ₂₀ H ₂₀ FNO ₅

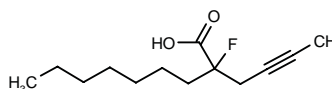
SOURCE – SmithKline Beecham.

REFERENCES

1. Bell, D. et al. (SmithKline Beecham plc) *Subst. benzopyran derivs. and their use as anticonvulsants.* WO 0000484.

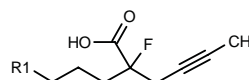
284773

2-Fluoro-2-heptyl-4-hexynoic acid



C13 H21 F O2; Mol wt: 228.3049

ACTION – Anticonvulsant that exhibits more potent anticonvulsant activity than valproic acid, as demonstrated against pentylenetetrazol-induced seizures (80% protection at 0.5 mmol/kg i.p. vs. 60% for valproic acid at 1.0 mmol/kg i.p.), and reduced teratogenic potential (0% fetuses exhibiting exencephaly at 1.0 mmol/kg vs. 50% for valproic acid at 3.0 mmol/kg). Other compounds from this series of α-fluoro alkynoic acid derivatives include the following:



Compound	R1	Formula
284774	H	C ₉ H ₁₃ FO ₂
284775	Et	C ₁₁ H ₁₇ FO ₂
284777	C ₅ H ₁₁	C ₁₄ H ₂₃ FO ₂

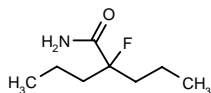
SOURCE – American Biogenetic Sciences.

REFERENCES

1. Nau, H. (American Biogenetic Sciences, Inc.) *α-Fluoro alkynoic acids with anticonvulsant activity*. WO 9967195.

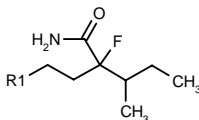
284778

2-Fluoro-2-propylpentanamide



C₈ H₁₆ F N O; Mol wt: 161.2184

ACTION – Anticonvulsant that exhibits more potent anticonvulsant activity than valproic acid and valpromide against pentylenetetrazol-induced seizures in mice (ED₅₀ = 0.16 mmol/kg i.p. vs. 0.61 and 0.29 mmol/kg i.p. for valproic acid and valpromide, respectively) and reduced sedation (TD₅₀ = 0.57 mmol/kg vs. 1.83 and 0.72 mmol/kg for valproic acid and valpromide, respectively, in the rotarod test) and teratogenic potential (0% fetuses exhibiting exencephaly at 3.0 mmol/kg i.v. vs. 37 and 6.5% for valproic acid and valpromide, respectively, at 3.0 mmol/kg i.v.). Other compounds from this series of 2-fluoro-2-alkyl alkanoamides include the following:



Compound	R1	Formula
284779	H	C ₈ H ₁₆ FNO
284780	Me	C ₉ H ₁₈ FNO

SOURCE – American Biogenetic Sciences.

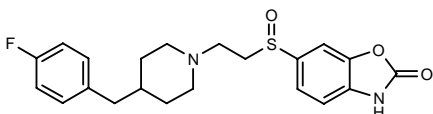
REFERENCES

1. Nau, H. (American Biogenetic Sciences, Inc.) *2-Fluoro-2-alkyl alkanoamides with anticonvulsant activity*. WO 9967199.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

284928

(+)-6-[2-[4-(4-Fluorobenzyl)piperidin-1-yl]ethylsulfanyl]-benzoxazol-2(3H)-one



C₂₁ H₂₃ F N₂ O₃ S; Mol wt: 402.4877

ACTION – NMDA receptor antagonist with high affinity and selectivity for the NR1A/2B subtype (IC₅₀ = 0.03 μM) relative to the NR1A/2A or NR1A/2C subtypes. *In vivo*, compound was shown to potentiate the contraversive rotations induced by L-DOPA in rats with 6-OHDA-induced lesions of the nigrostriatal dopamine system, with a minimum effective dose (MED) of 1 mg/kg p.o. Potentially useful for the treatment of Parkinson's disease, preferably in combination with L-DOPA, as well as chronic pain, depression and convulsions. A specifically claimed compound from a series of 4-benzylpiperidine alkylsulfoxide heterocycles.

SOURCES – CoCensys; Warner-Lambert.

REFERENCES

1. Wright, J.L. et al. (Warner-Lambert Co.;CoCensys, Inc.) *4-Benzyl piperidine alkylsulfoxide heterocycles and their use as subtype-selective NMDA receptor antagonists*. WO 0000197.

THERAPY OF DEGENERATIVE DISEASES OF THE NERVOUS SYSTEM

iPrP13

284648

L-Aspartyl-L-alanyl-L-prolyl-L-alanyl-L-alanyl-L-prolyl-L-alanyl-glycyl-L-prolyl-L-alanyl-L-valyl-L-prolyl-L-valine

C₅₁ H₈₁ N₁₃ O₁₆; Mol wt: 1132.2760

ACTION – Prion protein PrP^{Sc} analogue, a 13-residue β-sheet breaker peptide able to significantly delay the clinical symptoms of neurodegenerative diseases such as Creutzfeldt-Jakob disease, bovine spongiform encephalopathy and scrapie. Compound was able to concentration-dependently reduce the levels of protease-resistant peptide in scrapie-infected mouse brain (90% reduction following 48-h incubation with a 1,000-fold molar excess of compound) and in human brain tissues extracted postmortem from patients with sporadic and variant Creutzfeldt-Jakob disease (80% reduction after 48-h incubation with a 100-fold molar excess of compound). Peptide was also found to prevent the formation of PrP^{Sc}-like protein in a cellular model of familial prion disease using CHO cells. In mice infected with partially purified PrP^{Sc}, a significant delay in the development of symptoms of scrapie was seen when the PrP^{Sc} had been incubated for 48 h with an equimolar concentration of peptide. Treatment of infectious material with compound was also shown to reduce infectivity by 90-95%. Considered a prototype compound for the development of new treatments capable of preventing or reversing the conformational changes in PrP implicated in transmissible spongiform encephalopathies.

SOURCES – Ares-Serono; Axonyx; New York University, New York, NY (US).

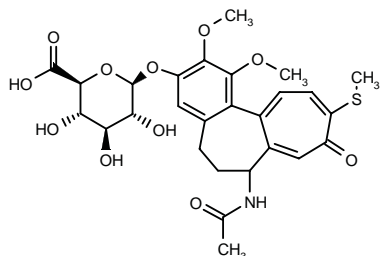
REFERENCES

1. Soto, C. et al. *Reversion of prion protein conformational changes by synthetic β-sheet breaker peptides*. Lancet 2000, 355(9199): 192.

ANTISPASTIC DRUGS AND DRUGS FOR MUSCLE SPASMS

284192

1-O-[7-(Acetylamino)-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-3-yl]-β-D-glucopyranuronic acid



C27 H31 N O11 S; Mol wt: 577.6039

ACTION – Muscle relaxant, a thiocolchicoside derivative proven to produce 78% inhibition of electrically stimulated polysynaptic reflexes in rats at a dose of 10 mg/kg i.p.

SOURCE – Sanofi-Synthélabo.

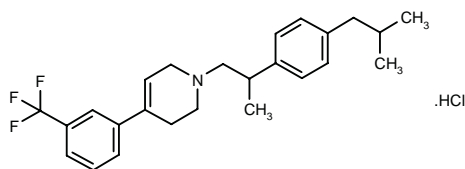
REFERENCES

1. Thenot, J.-P. et al. (Synthélabo) *Thiocolchicoside deriv., preparation and therapeutic application*. FR 2779147, WO 9961457.

COGNITION-ENHANCING DRUGS

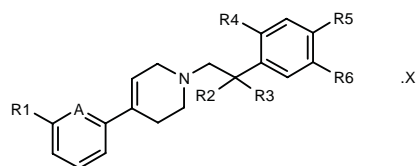
282527

1-[2-[4-(Isobutyl)phenyl]propyl]-4-[3-(trifluoromethyl)-phenyl]-1,2,3,6-tetrahydropyridine hydrochloride



C25 H30 F3 N . HCl; Mol wt: 437.9739

ACTION – Neurotrophic and neuroprotective agent with potential in the treatment of memory disorders, vascular dementia, postencephalitic disorders, poststroke disorders, brain trauma, cerebral anoxia, Alzheimer's disease, senile dementia, Huntington's disease, Parkinson's disease, AIDS-related dementia, cerebral edema and amyotrophic lateral sclerosis. Other compounds from this series of 4-aryl-1-phenylalkyl-1,2,3,6-tetrahydropyridines include the following:



Compound	R1	R2	R3	R4	R5	R6	A	X	Formula
282528	CF3	H	H	H	t-Bu	H	CH	HCl	C ₂₄ H ₂₈ F ₃ N.HCl
282529	CF3	H	H	H	4-Cl-Ph	H	CH		C ₂₆ H ₂₃ ClF ₃ N
282530	CF3	Me	Me	H	Ph	H	CH	HCl	C ₂₈ H ₂₈ F ₃ N.HCl
282532	CF3	H	H	H	OBu	H	CH	HCl	C ₂₄ H ₂₈ F ₃ NO.HCl
282533	CF3	H	H	H	3,5-(Cl)2-Ph	H	CH	HCl	C ₂₆ H ₂₂ Cl ₂ F ₃ N.HCl
282534	CF3	H	H	OMe	H	Ph	CH	HCl	C ₂₇ H ₂₆ F ₃ NO.HCl
282536	CF3	H	H	H	2-CF3-Ph	H	CH	HCl	C ₂₇ H ₂₄ ClF ₆ N.HCl
282537	Cl	Me	H	H	i-Bu	H	N	HCl	C ₂₃ H ₂₉ ClN ₂ .HCl

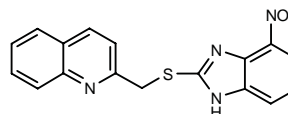
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Badone, D. et al. (Sanofi SA) *4-Aryl-1-phenylalkyl-1,2,3,6-tetrahydropyridines having neurotrophic and neuroprotective activity*. FR 2736053, US 5981754, WO 9701536.

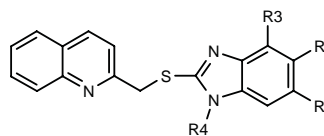
282849

2-(4-Nitro-1H-benzimidazol-2-ylsulfanylmethyl)quinoline



C17 H12 N4 O2 S; Mol wt: 336.3738

ACTION – An inhibitor of Ca²⁺-calmodulin-dependent phosphodiesterase (PDE1; 88% inhibition at 100 μM using enzyme from bovine brain) with potential in the treatment of cerebral ischemia, vascular dementia, senile dementia and memory and learning impairment. A representative compound from a series of benzimidazole derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
282850	H	H	Me	H	C ₁₈ H ₁₅ N ₃ S
282851	H	Me	Me	H	C ₁₉ H ₁₇ N ₃ S
282852	Cl	H	Cl	H	C ₁₇ H ₁₁ Cl ₂ N ₃ S
282853	OMe	OMe	H	H	C ₁₉ H ₁₇ N ₃ O ₂ S
282854	Me	H	H	Et	C ₂₀ H ₁₉ N ₃ S
282855	H	NHCONH2	H	H	C ₁₈ H ₁₅ N ₅ OS
282856	H	CH2OH	H	H	C ₁₈ H ₁₅ N ₃ OS

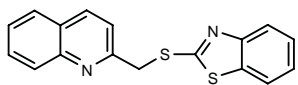
SOURCES – Sagami; Taisho.

REFERENCES

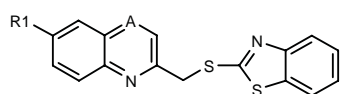
1. Ohta, T. et al. (Taisho Pharmaceutical Co., Ltd.; Sagami Chemical Research Center) *Benzimidazole derivs*. JP 1999279175.

282882

2-(2-Benzothiazolylsulfanylmethyl)quinoline

C₁₇H₁₂N₂S₂; Mol wt: 308.4278

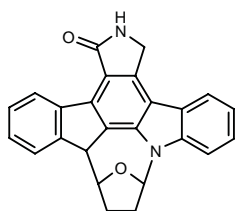
ACTION – An inhibitor of Ca²⁺-calmodulin-dependent phosphodiesterase (PDE1; 57% inhibition at 100 μM using enzyme from bovine brain) with potential in the treatment of cerebral ischemia, vascular dementia, senile dementia and memory and learning impairment. A representative compound from a series of benzothiazole derivatives, wherein the following are also included:



Compound	R1	A	Formula
282883	H	N	C ₁₆ H ₁₁ N ₃ S ₂
282884	Cl	CH	C ₁₇ H ₁₁ ClN ₂ S ₂

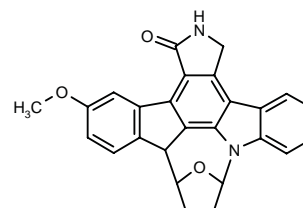
SOURCES – Sagami; Taisho.**REFERENCES**

1. Ohta, M. et al. (Taisho Pharmaceutical Co., Ltd.; Sagami Chemical Research Center) *Benzothiazole derivs.* JP 1999279177.

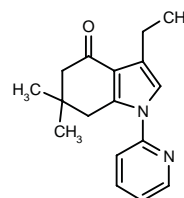
2841979,12-Epoxy-1,2,3,9,10,11,12,12a-octahydroindeno-[1,2,3-*fg*]indolo[3,2,1-*k*]pyrrolo[3,4-*l*][1]benzazocin-1-oneC₂₅H₁₈N₂O₂; Mol wt: 378.4292

ACTION – Agent for enhancing trophic factor-induced activities of trophic factor-responsive cells, e.g., cholinergic neurons, as well as for promoting the survival of other neuronal cell types, e.g., dopaminergic and glutamatergic cells, and also shown to inhibit kinases such as trkA kinase (IC₅₀ = 13 nM), vascular endothelial growth factor (VEGF) receptor kinase (IC₅₀ = 30 nM) and, to a lesser extent, protein kinase C (IC₅₀ = 1300 nM) and platelet-derived growth factor (PDGF) receptor kinase (IC₅₀ = 1383 nM). *In vitro*, compound was also shown to inhibit nerve growth factor (NGF)-stimulated trk phosphorylation in NIH3T3 cells (76-100% inhibition at 1000 nM). Compound also increased choline acetyltransferase (ChAT) activity in a dissociated rat embryonic spinal cord culture assay, with a maximal increase of 139% at 300 nM. Potentially useful for the treatment or prevention of Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, stroke, Huntington's disease, epilepsy, multiple sclerosis, peripheral neuropathy or brain

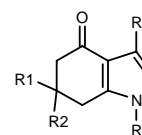
or spinal cord injury, as well as prostate cancer and benign prostatic hyperplasia, angiogenic disorders, rheumatoid arthritis, pulmonary fibrosis, atherosclerosis and restenosis. Another compound from this series of bridged indenopyrrolocarbazoles is:

**284198:** C₂₆H₂₀N₂O₃**SOURCE** – Cephalon.**REFERENCES**

1. Singh, J. et al. (Cephalon, Inc.) *Bridged indenopyrrolocarbazoles.* WO 9962523.

2842253-Ethyl-6,6-dimethyl-1-(2-pyridyl)-4,5,6,7-tetrahydro-1*H*-indol-4-oneC₁₇H₂₀N₂O; Mol wt: 268.3580

ACTION – Agent for enhancing cognition, particularly for the treatment of Alzheimer's disease, with selective affinity for GABA_A α5 receptors. A representative compound from a series of tetrahydroindolone derivatives, wherein the following are also included:



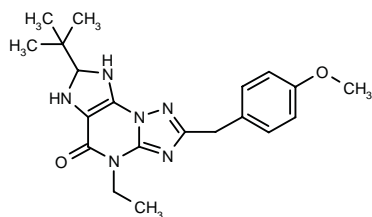
Compound	R1	R2	R3	R4	Formula
284226	Me	Me	2-pyrimidinyl	Et	C ₁₆ H ₁₉ N ₃ O
284227	Me	Me	4-Cl-Ph	Et	C ₁₈ H ₂₀ ClNO
284228	Me	Me	2-Pyr	2-thiazolyl	C ₁₈ H ₁₇ N ₃ OS
284229	Me	Me	2-Pyr	2-Pyr-NH	C ₂₀ H ₂₀ N ₄ O
284230	Me	Me	5-Cl-2-Pyr	2-thiazolyl	C ₁₈ H ₁₆ ClN ₃ OS
284231	Me	Me	2-Pyr	3-Me-1,2,4-oxadiazol-5-yl	C ₁₈ H ₁₈ N ₄ O ₂
284232	H	Pr	2-Pyr	t-Bu	C ₂₀ H ₂₈ N ₂ O

SOURCE – Merck Sharp & Dohme.**REFERENCES**

1. Broughton, H.B. et al. (Merck Sharp & Dohme Ltd.) *Tetrahydroindolone derivs. as GABAα5 ligands for enhancing cognition.* WO 9962899.

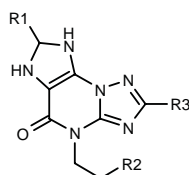
284589

7-*tert*-Butyl-4-ethyl-2-(4-methoxybenzyl)-5,6,7,8-tetrahydro-4*H*-[1,2,4]triazolo[5,1-*b*]purin-5-one



C20 H26 N6 O2; Mol wt: 382.4654

ACTION – Adenosine A₁ receptor antagonist ($K_i = 2.1$ nM) with potential in the treatment of CNS disorders such as Alzheimer's disease, as well as cardiovascular and renal disorders. Other compounds from this series of imidazo-triazolopyrimidines include the following:



Compound	R1	R2	R3	Formula
284590	Pr	Me	cyclopentyl	C ₁₇ H ₂₆ N ₆ O
284591	Me	Me	CH ₂ Ph	C ₁₇ H ₂₀ N ₆ O
284592	Me	H	CH ₂ CH ₂ Ph	C ₁₇ H ₂₀ N ₆ O
284593	Pr	H	CH ₂ CH ₂ Ph	C ₁₉ H ₂₄ N ₆ O
284594	<i>t</i> -Bu	H	4-OH-PhCH ₂	C ₁₉ H ₂₄ N ₆ O ₂
284595	cyclopentyl	H	CH ₂ OPh	C ₂₀ H ₂₄ N ₆ O ₂
284596	cyclopentyl	H	1-pyrrolyl-CH ₂	C ₁₈ H ₂₃ N ₇ O
284597	Me	Me	2-furyl	C ₁₄ H ₁₆ N ₆ O ₂
284598	Pr	Me	2-furyl	C ₁₆ H ₂₀ N ₆ O ₂

SOURCE – Boehringer Ingelheim.

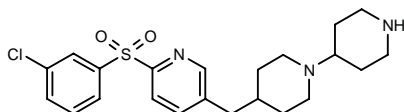
REFERENCES

1. Blech, S. et al. (Boehringer Ingelheim Pharma KG) *Imidazotriazolopyrimidines used as drug having an adenosine antagonist activity*. DE 19826843, WO 9965912.

284698

4-[6-(3-Chlorophenylsulfonyl)pyridin-3-ylmethyl]-1-(piperidin-4-yl)piperidine

(3-Chlorophenyl)[5-[1-(piperidin-4-yl)piperidin-4-yl-methyl]pyridin-2-yl] sulfone



C22 H28 Cl N3 O2 S; Mol wt: 434.0012

ACTION – Muscarinic antagonist with a K_i value of 1.5 nM for cloned human M₂ receptors versus a K_i of 917 nM for M₁ receptors, expected to be of use in the treatment of cognitive and neurodegenerative disorders such as Alzheimer's disease.

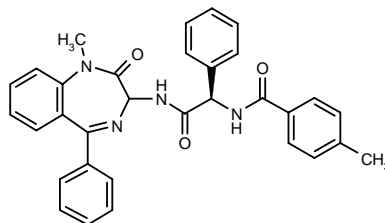
SOURCE – Schering-Plough.

REFERENCES

1. Kozlowski, J.A. et al. (Schering Corp.) *Muscarinic antagonists*. WO 0000488.

284910

*N*²-(4-Methylbenzoyl)-*N*¹-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-3-yl)-2(*R*)-phenylglycinamide



C32 H28 N4 O3; Mol wt: 516.5982

ACTION – Agent for the treatment of Alzheimer's disease shown to inhibit β -amyloid peptide production in K293 cells stably transfected with the gene for amyloid precursor protein 751 (APP751) containing the double mutation Lys651, Met652 to Asn651, Leu652 (also known as the Swedish mutation) by at least 30% at a concentration of 10 μ g/ml.

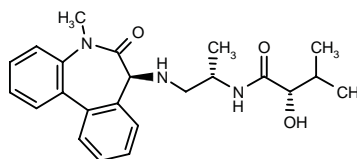
SOURCES – Elan; Lilly.

REFERENCES

1. Thompson, R.C. et al. (Eli Lilly and Company; Elan Corporation, plc) *Cpds. for inhibiting β -amyloid peptide release and/or its synthesis*. WO 9967221.

284912

2(*S*)-Hydroxy-3-methyl-*N*-[1(*S*)-methyl-2-[5-methyl-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7(*S*)-ylamino]ethyl]-butylamide



C23 H29 N3 O3; Mol wt: 395.5001

ACTION – Agent for the treatment of Alzheimer's disease shown to inhibit β -amyloid peptide production in K293 cells stably transfected with the gene for amyloid precursor protein 751 (APP751) containing the double mutation Lys651, Met652 to Asn651, Leu652 (also known as the Swedish mutation) by at least 30% at a concentration of 10 μ g/ml.

SOURCES – Elan; Lilly.

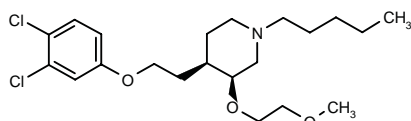
REFERENCES

1. Audia, J.E. et al. (Eli Lilly and Company; Elan Corporation, plc) *Cpds. for inhibiting β -amyloid peptide release and/or its synthesis*. WO 9967220.

TREATMENT OF CEREBROVASCULAR DISEASES

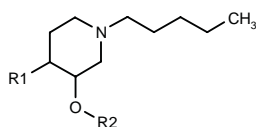
282539

(±)-*cis*-4-[2-(3,4-Dichlorophenoxy)ethyl]-3-(2-methoxyethoxy)-1-pentylpiperidine



C₂₁ H₃₃ Cl₂ N O₃; Mol wt: 418.4017

ACTION – Agent for the treatment of stroke, anoxia, ischemia, migraine, psychosis or epilepsy that acts by blocking N-type calcium channels, as demonstrated by an IC₅₀ value of 0.3 μM for inhibition of ⁴⁵Ca²⁺ uptake into chick cortical synaptosomes. Compound is also reported to block sodium channels at concentrations of 1-10 μM in electrophysiological studies. Within this series of piperidine derivatives, the following are also included:



Compound	R1	R2	Isomer	Formula
282540	3,4-(Cl)2-PhOCH2CH2	Me	(±)-trans	C ₁₉ H ₂₉ Cl ₂ NO ₂
282541	2,3-(Me)2-PhOCH2CH2	Me	(±)-cis	C ₂₁ H ₃₅ NO ₂
282542	3,4-Cl-PhOCH2CH2	CH2CH2OMe	(±)-trans	C ₂₁ H ₃₃ Cl ₂ NO ₃
282543	3,4-Cl-PhOCH2CH2	Ac	(±)-trans	C ₂₀ H ₂₉ Cl ₂ NO ₃
282544	3-(i-PrO)-PhOCH2CH2	CH2CH2OMe	(±)-trans	C ₂₄ H ₄₁ NO ₄
282545	4-(PhO)-PhO	CH2CH2OMe	(±)-trans	C ₂₅ H ₃₅ NO ₄
282547	CH2CH2N(Ph)2	Me	(±)-trans	C ₂₅ H ₃₆ N ₂ O
282548	CH2CH2N(Ph)2	Me	(±)-cis	C ₂₅ H ₃₆ N ₂ O
282549	2-Ph-PhOCH2CH2	Me	(±)-cis	C ₂₅ H ₃₆ NO ₂
282550	4-Cl-PhCH2S	CH2CH2OMe	(±)-trans	C ₂₀ H ₃₂ ClNO ₂ S
282551	2-(PhCH2)-PhOCH2CH2	Me	(±)-cis	C ₂₆ H ₃₇ NO ₂
282553	2-(PhCH2)-PhOCH2CH2	Me	(±)-trans	C ₂₆ H ₃₇ NO ₂
282554	2-(PhCH2O)-PhO	CH2CH2OMe	(±)-trans	C ₂₆ H ₃₇ NO ₄
282555	CH2CH2N(Ph)2	CH2CH2OMe	(±)-trans	C ₂₇ H ₄₀ N ₂ O ₂

SOURCE – NeuroSearch.

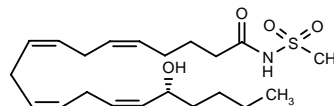
REFERENCES

1. Axelsson, O. et al. (NeuroSearch A/S) Piperidine cpds. as calcium channel blockers. US 5981539, WO 9710212.

283716

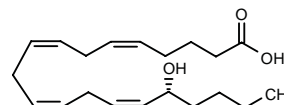
16(*R*)-Hydroxy-*N*-(methanesulfonyl)-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-icosatetraenamide

16(*R*)-HETE-sulfonamide

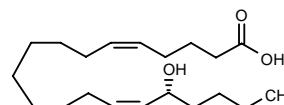


C₂₁ H₃₅ N O₄ S; Mol wt: 397.5765

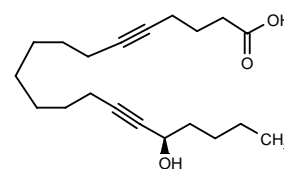
ACTION – Antiinflammatory agent, an analogue of 16-hydroxyeicosatetraenoic acid (16-HETE) shown to inhibit fMLP-stimulated neutrophil aggregation *in vitro* with comparable potency to 16(*R*)-HETE. Methods of treating thromboembolic stroke using agonists such as the title compound, in combination with a thrombolytic agent such as tPA, as well as inflammatory disorders such as rheumatoid arthritis, osteoarthritis, allergic rhinitis, psoriasis, dermatitis, ischemia-induced myocardial injury, reperfusion injury, gout, asthma, adult respiratory distress syndrome, atherosclerosis, meningitis, pancreatitis, ulcerative colitis, etc., are specifically claimed. Other compounds from this series of 16-HETE analogues include the following:



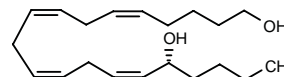
283717: C₂₀ H₃₂ O₃



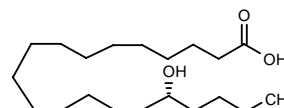
283718: C₂₀ H₃₆ O₃



283719: C₂₀ H₃₂ O₃



283720: C₂₀ H₃₄ O₂



283721: C₂₀ H₄₀ O₃

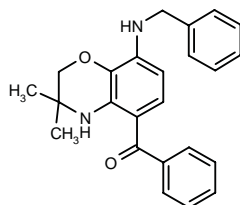
SOURCES – New York Medical College, Valhalla, NY (US); University of Texas System, Austin, TX (US); University of Vermont, Burlington, VT (US).

REFERENCES

1. Falck, J.R. et al. (University of Vermont;University of Texas System;New York Medical College) *Novel analogs of 16-hydroxyeicosatetraenoic acid*. WO 9959964.

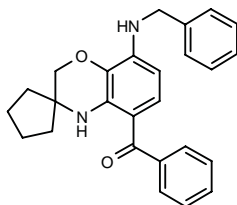
284012

1-[8-(Benzylamino)-3,3-dimethyl-3,4-dihydro-2H-1,4-benzoxazin-5-yl]-1-phenylmethanone



C24 H24 N2 O2; Mol wt: 372.4656

ACTION – Antioxidant shown to protect against L-homo-cysteinic acid-induced toxicity in murine hippocampal HT-22 cells ($PC_{50} = 3.1\text{--}7.1 \mu\text{M}$), while showing no cytotoxicity in these cells (TC_{50} and maximum tolerated dose $> 250 \mu\text{M}$). Potentially useful in the treatment of cerebral ischemia, epilepsy, neurodegenerative disorders such as Alzheimer's disease, Pick's disease, Parkinson's disease, Huntington's disease and Down's syndrome, as well as atherosclerosis and cancer. Another compound from this series of 8-amino-1,4-benzoxazine derivatives is:



284013: C26 H26 N2 O2

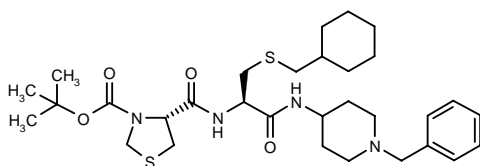
SOURCE – ADIR.

REFERENCES

1. Fleury, M.B. et al. (ADIR et Cie.) *Novel 8-amino-1,4-benzoxazine cpds., preparation method and pharmaceutical compns. containing them*. FR 2779144, WO 9962889.

284877

*N*¹-(1-Benzylpiperidin-4-yl)-*N*²-[3-(*tert*-butoxycarbonyl)-thiazolidin-4(*R*)-ylcarbonyl]-*S*-(cyclohexylmethyl)-L-cysteineamide



C31 H48 N4 O4 S2; Mol wt: 604.8762

ACTION – N-type calcium channel antagonist with potential in the treatment or prevention of stroke, transient ischemic attacks, epilepsy, asthma, frequent urination and for use as analgesics. A representative compound from a series of amino acid derivatives.

SOURCE – Ono.

REFERENCES

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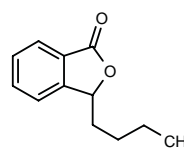
3-*n*-BUTYLPHTHALIDE

284092

(±)-3-Butyl-1(3*H*)-isobenzofuranone

(±)-3-Butyl-2-benzofuran-1(3*H*)-one

NBP



C12 H14 O2; Mol wt: 190.2406

ACTION – Neuroprotective and cerebral antiischemic agent isolated from several plants including *Apium graveolens*, *Angelica amiloba*, *Ligusticum sinensis* and *Ligusticum wallichii*. In a model of cerebral ischemia in rats subjected to middle cerebral artery occlusion, compound (10-20 mg/kg i.p. or 40-100 mg/kg p.o.) was able to increase regional cerebral blood flow in the ischemic zone, reduce infarct area, protect the integrity of the blood-brain barrier, prolong life span and decrease neurological deficit scores following stroke. *In vitro* studies demonstrated that it inhibits cytotoxicity induced by potassium chloride, NMDA or hypoxia/hypoglycemia in primary rat cortical neurons; it was also found to inhibit intracellular lactate dehydrogenase (LDH) release induced by NMDA ($IC_{50} = 4.89 \mu\text{M}$), reduce NMDA-induced cell death ($IC_{50} = 44.37 \mu\text{M}$) and protect against apoptosis induced by hypoxia/hypoglycemia. It appears to act primarily by improving brain energy metabolism. Compound showed no marked acute toxicity in mice or chronic toxicity in dogs and no reproductive toxicity or mutagenicity was observed. Clinical trials in patients with stroke are under way.

SOURCES – Chinese Academy of Medical Sciences, Beijing (CN); Institute of Materia Medica, Beijing (CN).

REFERENCES

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4. Chong, Z.Z. and Feng, Y.P. *Effects of dl-3-n-butylphthalide on production of TXB2 and 6-keto-PGF_{1α} in rat brain during focal cerebral ischemia and reperfusion*. Acta Pharmacol Sin 1997, 18: 505.

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8. Dong, G.X. and Feng, Y.P. *Anticonvulsant effects of 3-n-butylphthalide*. Chin Pharmacol Bull 1999, 15: 88.

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19. Xu, H.L. and Feng, Y.P. *Effects of 3-n-butylphthalide on pial arterioles in focal cerebral ischemia rats*. Acta Pharm Sin 1999, 34: 172.

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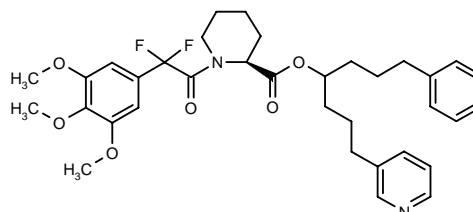
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MONOGRAPH – Wang, X.-W. 3-n-Butylphthalide. Drugs Fut 2000, 25(1): 0016.

MISCELLANEOUS NEUROLOGIC DRUGS

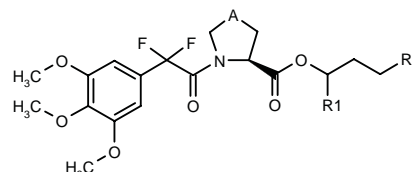
284340

1-[2,2-Difluoro-2-(3,4,5-trimethoxyphenyl)acetyl]piperidine-2(S)-carboxylic acid 4-phenyl-1-[3-(3-pyridinyl)propyl]butyl ester



C35 H42 F2 N2 O6; Mol wt: 624.7208

ACTION – Neurotrophic agent that binds to immunophilins such as the FK-506-binding protein FKBP12 and inhibits peptidylprolyl isomerase (PPLase or rotamase) activity, giving a K_i value of 19 nM and producing 98% inhibition at 10 μM. This nonimmunosuppressive compound stimulates neurite outgrowth, as demonstrated in rat pheochromocytoma PC-12A cells, and may also be useful for reversing multidrug resistance (MDR) in cancer chemotherapy and in the treatment of HIV infection. Other exemplified α,α-difluoroacetamide compounds include the following:



Compound	R1	R2	A	Formula
284341	3-Pyr-(CH ₂) ₃	CH ₂ Ph	-CH ₂ -	C ₃₄ H ₄₀ F ₂ N ₂ O ₆
284342	Ph	Ph	-CH ₂ -	C ₃₁ H ₃₃ F ₂ N ₂ O ₆
284343	H	3,4,5-(MeO) ₃ -Ph	-(CH ₂) ₂ -	C ₂₉ H ₃₇ F ₂ N ₂ O ₉

SOURCE – Bristol-Myers Squibb.

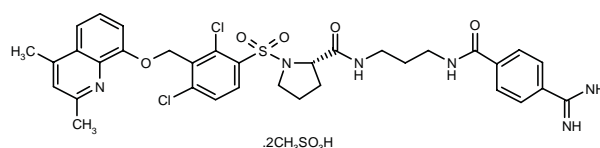
REFERENCES

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LF-16-0687MS*

267330

N-[3-(4-Amidinobenzamido)propyl]-1-[2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)phenylsulfonyl]-L-prolinamide bis(methanesulfonate)



C34 H36 Cl2 N6 O5 S . 2 C H4 O3 S; Mol wt: 903.8786

ACTION – Potent, nonpeptide bradykinin B₂ receptor antagonist with K_i values of 0.67, 1.74 and 1.37 nM, respectively, for binding to recombinant human, rat and guinea pig B₂ receptors expressed in CHO cells, and K_i values of 0.89, 0.28 and 0.98 nM, respectively, for binding to native B₂ receptors from human umbilical vein, rat uterus and guinea pig ileum. Compound at concentrations of up to 10 µM, had no significant effect at human B₁ receptors or a number of other receptors, enzymes and ion channels, except for human muscarinic M₂ and M₁ receptors (IC₅₀ = 0.30 and 0.46 µM, respectively). In *in vitro* functional tests, it inhibited bradykinin-induced phosphoinositide production in INT407 cells with pK_B values of 8.5-8.7; competitive antagonism of bradykinin-mediated contractions was also observed in human umbilical vein, rat uterus and guinea pig ileum (pA₂ = 9.1, 7.7 and 9.1, respectively). *In vivo*, at doses of 1.2-120 nmol/kg/min it provided dose-dependent and rapid-onset blockade of the hypotensive response induced by bradykinin in rats, and at a dose of 1.1 µmol/kg s.c. it inhibited bradykinin-induced edema in pancreas, stomach and duodenum of rats (56-69% reduction). Compound was also seen to reduce brain edema in rats with closed-head trauma (64-68% reduction at 100 µg/kg/min) and to afford significant improvement in neurological function, with no significant effect on mean arterial blood pressure. Potentially useful for the treatment of cerebral edema secondary to traumatic brain injury.

SOURCE – Fournier.

REFERENCES

1. Dodey, P. et al. (Fournier Industrie et Santé) *Novel N-benzenesulphonyl-L-proline derivs., method for preparing and therapeutic use*. EP 0944618, WO 9824783.
2. Pruneau, D. et al. *Effect of LF 16-0687MS, a new nonpeptide bradykinin B-2 receptor antagonist, in a rat model of closed head trauma*. J Neurotrauma 1999, 16(11): 1057.
3. Pruneau, D. et al. *Pharmacological profile of LF 16-0687, a new potent non-peptide bradykinin B-2 receptor antagonist*. Immunopharmacology 1999, 43(2-3): 187.
4. Schulz, J. et al. *LF 16-0687, a new non-peptide bradykinin B2 receptor antagonist, reduces vasogenic brain oedema after cortical cold injury in rats*. J Cereb Blood Flow Metab 1999, 19(Suppl. 1): Abst 675.
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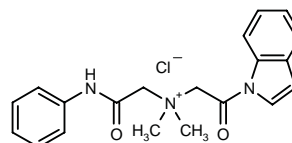
*Identified compound **267330** (see **266223**) Drug Data Rep 1998, 020(09): 0747.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

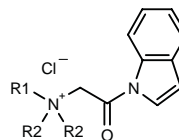
284194

N-(1*H*-Indol-1-ylcarbonylmethyl)-*N,N*-dimethyl-*N*-(*N*-phenylcarbamoylmethyl)ammonium chloride



C20 H22 Cl N3 O2; Mol wt: 371.8658

ACTION – Antitussive agent whose activity was demonstrated against citric acid-induced cough in guinea pigs; pretreatment with an aerosol containing 10 mg/ml of compound immediately before citric acid challenge inhibited cough responses by 56%. Other specifically claimed compounds from this series of quaternary ammonium derivatives include the following:



Compound	R1	R2	Formula
284195	1-indolyl-COCH2	Me	C ₂₂ H ₂₂ ClN ₃ O ₂
284196	Et	Et	C ₁₃ H ₁₇ ClN ₂ O

SOURCE – Nortran.

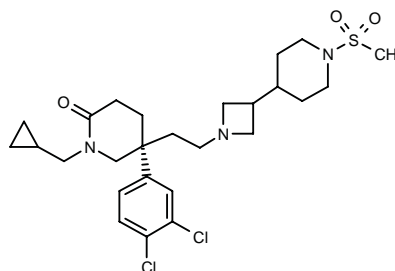
REFERENCES

1. Page, C.P. et al. (Nortran Pharmaceuticals Inc.) *Quaternary ammonium cpds. as anti-tussive agents*. WO 9964398.

ASTHMA THERAPY

283744

1-(Cyclopropylmethyl)-5(*S*)-(3,4-dichlorophenyl)-5-[2-[3-[1-(methylsulfonyl)piperidin-4-yl]azetidin-1-yl]ethyl]-piperidin-2-one



C26 H37 Cl2 N3 O3 S; Mol wt: 542.5683

ACTION – Potent, nonpeptide bradykinin B₂ receptor antagonist with K_i values of 0.67, 1.74 and 1.37 nM, respectively, for binding to recombinant human, rat and guinea pig B₂ receptors expressed in CHO cells, and K_i values of 0.89, 0.28 and 0.98 nM, respectively, for binding to native B₂ receptors from human umbilical vein, rat uterus and guinea pig ileum. Compound at concentrations of up to 10 µM, had no significant effect at human B₁ receptors or a number of other receptors, enzymes and ion channels, except for human muscarinic M₂ and M₁ receptors (IC₅₀ = 0.30 and 0.46 µM, respectively). In *in vitro* functional tests, it inhibited bradykinin-induced phosphoinositide production in INT407 cells with pK_B values of 8.5-8.7; competitive antagonism of bradykinin-mediated contractions was also observed in human umbilical vein, rat uterus and guinea pig ileum (pA₂ = 9.1, 7.7 and 9.1, respectively). *In vivo*, at doses of 1.2-120 nmol/kg/min it provided dose-dependent and rapid-onset blockade of the hypotensive response induced by bradykinin in rats, and at a dose of 1.1 µmol/kg s.c. it inhibited bradykinin-induced edema in pancreas, stomach and duodenum of rats (56-69% reduction). Compound was also seen to reduce brain edema in rats with closed-head trauma (64-68% reduction at 100 µg/kg/min) and to afford significant improvement in neurological function, with no significant effect on mean arterial blood pressure. Potentially useful for the treatment of cerebral edema secondary to traumatic brain injury.

SOURCE – Fournier.

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1. Dodey, P. et al. (Fournier Industrie et Santé) *Novel N-benzenesulphonyl-L-proline derivs., method for preparing and therapeutic use*. EP 0944618, WO 9824783.
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5. Shapira, Y. et al. *LF 16.0687, a new nonpeptide bradykinin B2 receptor antagonist, reduces cerebral edema in a rat model of closed head trauma*. Anesthesiology 1999, 91(3A): A733.

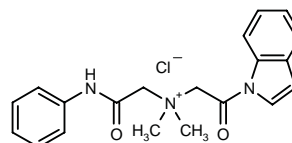
*Identified compound **267330** (see **266223**) Drug Data Rep 1998, 020(09): 0747.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

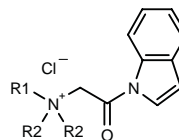
284194

N-(1*H*-Indol-1-ylcarbonylmethyl)-*N,N*-dimethyl-*N*-(*N*-phenylcarbamoylmethyl)ammonium chloride



C20 H22 Cl N3 O2; Mol wt: 371.8658

ACTION – Antitussive agent whose activity was demonstrated against citric acid-induced cough in guinea pigs; pretreatment with an aerosol containing 10 mg/ml of compound immediately before citric acid challenge inhibited cough responses by 56%. Other specifically claimed compounds from this series of quaternary ammonium derivatives include the following:



Compound	R1	R2	Formula
284195	1-indolyl-COCH2	Me	C ₂₂ H ₂₂ ClN ₃ O ₂
284196	Et	Et	C ₁₃ H ₁₇ ClN ₂ O

SOURCE – Nortran.

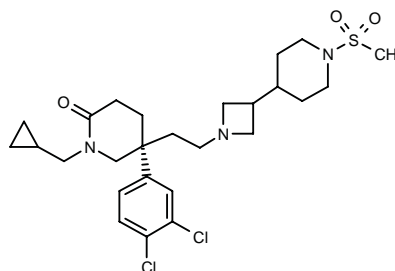
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ASTHMA THERAPY

283744

1-(Cyclopropylmethyl)-5(*S*)-(3,4-dichlorophenyl)-5-[2-[3-[1-(methylsulfonyl)piperidin-4-yl]azetidin-1-yl]ethyl]-piperidin-2-one



C26 H37 Cl2 N3 O3 S; Mol wt: 542.5683

ACTION – Tachykinin antagonist, a specifically claimed compound from a series of piperidone derivatives reported to possess improved potency and/or selectivity for the NK₂ receptor, as well as to have increased metabolic stability, compared to previously reported structurally related compounds. Compound exhibited a pIC₅₀ of 8.4 against [³H]-NKA binding to human NK₂ receptors cloned in CHO cells. Potentially useful in the treatment of asthma, arthritis, psoriasis and inflammatory bowel disease, as well as anxiety, depression, dementia, psychosis, irritable bowel syndrome, gastroesophageal reflux, Crohn's disease, urinary incontinence, chronic obstructive airways disease, eczema, contact dermatitis, rhinitis, peripheral neuropathy, postherpetic neuralgia, cough and acute or chronic pain.

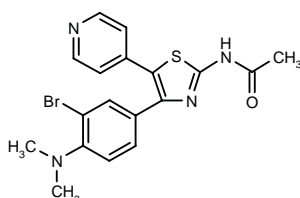
SOURCE – Pfizer.

REFERENCES

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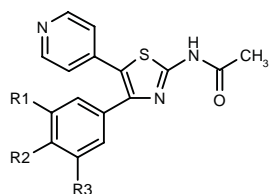
284284

N-[4-[3-Bromo-4-(dimethylamino)phenyl]-5-(4-pyridyl)-thiazol-2-yl]acetamide



C18 H17 Br N4 O S; Mol wt: 417.3293

ACTION – Agent for the treatment of obstructive or inflammatory airways diseases, a potent inhibitor of human adenosine A₃ receptor activation (IC₅₀ = 0.15 nM) with 10,000-fold selectivity over the A₁ receptor. Other compounds from this series of aryl pyridyl thiazoles include the following:



Compound	R1	R2	R3	Formula
284285	H	Me	H	C ₁₇ H ₁₅ N ₃ OS
284286	Me	H	Me	C ₁₈ H ₁₇ N ₃ OS
284287	Me	Me	H	C ₁₈ H ₁₇ N ₃ OS
284288	H	OBu	H	C ₂₀ H ₂₁ N ₃ O ₂ S
284289	Me	H	H	C ₁₇ H ₁₅ N ₃ OS
284290	Cl	H	H	C ₁₆ H ₁₂ ClN ₃ OS
284585	Cl	Cl	H	C ₁₆ H ₁₁ Cl ₂ N ₃ OS

Certain compounds within the scope of this patent inhibit the activation of adenosine A_{2B} receptors and/or TNF-α production.

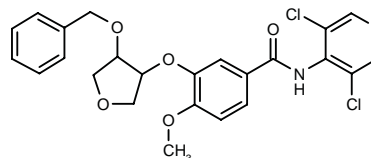
SOURCE – Novartis.

REFERENCES

1. Heng, R. et al. (Novartis AG) *Aryl pyridinyl thiazoles*. WO 9964418.

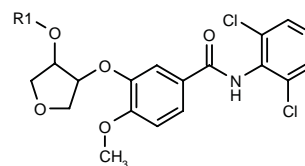
284317

3-[4-(Benzyloxy)tetrahydrofuran-3-yloxy]-*N*-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide

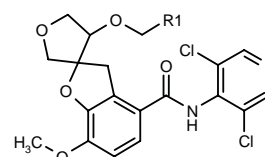


C24 H22 Cl2 N2 O5; Mol wt: 489.3528

ACTION – Selective inhibitor of phosphodiesterase type 4 (PDE4; -logIC₅₀ = 8.70) with potential in the treatment of asthma and other respiratory tract disorders. Within this series of tetrahydrofuranyloxy-substituted benzamide derivatives, the following are also included:



Compound	R1	Formula
284318	Me	C ₁₈ H ₁₈ Cl ₂ N ₂ O ₅
284319	Et	C ₁₉ H ₂₀ Cl ₂ N ₂ O ₅
284322	H	C ₁₇ H ₁₆ Cl ₂ N ₂ O ₅
284323	CH ₂ SMc	C ₁₉ H ₂₀ Cl ₂ N ₂ O ₅ S



Compound	R1	Formula
284320	H	C ₁₉ H ₁₈ Cl ₂ N ₂ O ₅
284321	Ph	C ₂₆ H ₂₂ Cl ₂ N ₂ O ₅

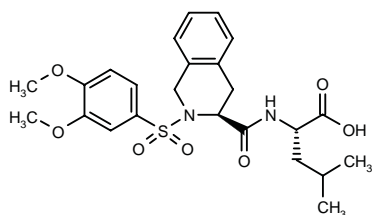
SOURCE – Byk Gulden.

REFERENCES

1. Martin, T. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Benzamides with tetrahydrofuranyloxy substituents as phosphodiesterase 4 inhibitors*. WO 9964414.

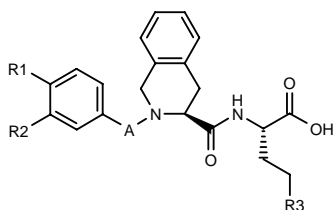
284405

N-[2-(3,4-Dimethoxyphenylsulfonyl)-1,2,3,4-tetrahydro-isoquinolin-3(S)-ylcarbonyl]-L-leucine

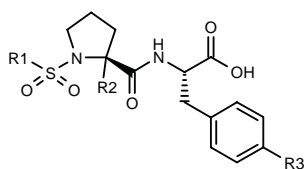


C24 H30 N2 O7 S; Mol wt: 490.5740

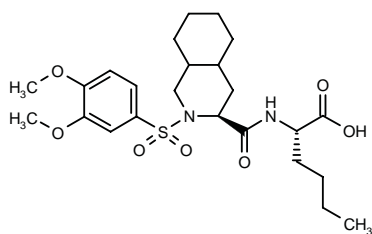
ACTION – Cell adhesion inhibitor that acts as an antagonist of VLA-4 ($\alpha_4\beta_1$) integrin and/or $\alpha_4\beta_7$ integrin, blocking the binding of VLA-4 and/or $\alpha_4\beta_7$ to their ligands, i.e., VCAM-1, fibronectin and MadCAM-1. As such, it is considered useful in the treatment of asthma, allergic rhinitis, multiple sclerosis, atherosclerosis, inflammatory bowel disease, etc. Other specifically claimed heterocyclic amides include the following:



Compound	R1	R2	R3	A1	Formula
284406	OMe	OMe	CH2NH-C(=NH)NH2	SO2	C ₂₄ H ₃₁ N ₅ O ₇ S
284407	Ph	H	Et	CO	C ₂₉ H ₃₀ N ₂ O ₄
284408	OMe	OMe	SMe	SO2	C ₂₃ H ₂₈ N ₂ O ₇ S ₂
284409	Cl	Cl	Et	SO2	C ₂₂ H ₂₄ Cl ₂ N ₂ O ₅ S
284410	H	NO2	Et	SO2	C ₂₂ H ₂₅ N ₃ O ₇ S



Compound	R1	R2	R3	Formula
284413	3-F-Ph	H	H	C ₂₀ H ₂₁ FN ₂ O ₅ S
284414	4-(PhSO2)-2-thienyl	H	t-BuO	C ₂₈ H ₃₂ N ₂ O ₈ S ₃
284415	3-(CO2Et)-Ph	H	t-BuO	C ₂₇ H ₃₄ N ₂ O ₈ S
284416	3-CF3-Ph	Me	NO2	C ₂₂ H ₂₂ F ₃ N ₃ O ₇ S
284417	3,5-(Cl)2-Ph	Me	4-CN-PhO	C ₂₈ H ₂₅ Cl ₂ N ₃ O ₆ S



284412: C24 H36 N2 O7 S

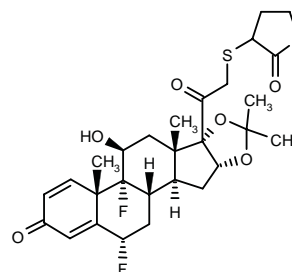
SOURCE – Merck & Co.

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1. Durette, P.L. et al. (Merck & Co., Inc.) *Heterocyclic amide cpds. as cell adhesion inhibitors*. WO 9964395.

284560

6 α ,9-Difluoro-11 β -hydroxy-16 α ,17-(isopropylidenedioxy)-21-(2-oxotetrahydrofuran-3-ylsulfanyl)pregna-1,4-diene-3,20-dione



C28 H34 F2 O7 S; Mol wt: 552.6316

ACTION – Glucocorticoid receptor agonist with nanomolar affinity for the human receptor ($IC_{50} = 3.4$ nM) and an ideal lung-selective antedrug profile of rapid inactivation in plasma combined with high stability in the target tissue. Potentially useful as a topical antiasthmatic agent.

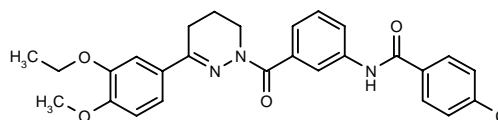
SOURCE – Glaxo Wellcome.

REFERENCES

1. Biggadike, K. and Farrell, R.M. (Glaxo Wellcome Inc.) *21-(2-Oxo-tetrahydrofuran)-thio pregnane derivs., a process for their production and pharmaceutical compsns. containing them*. US 6013244, WO 9724367.
2. Biggadike, K. et al. *Selective plasma hydrolysis of glucocorticoid gamma-lactones and cyclic carbonates by the enzyme paraoxonase: An ideal plasma inactivation mechanism*. J Med Chem 2000, 43(1): 19.

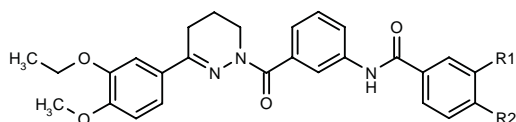
284600

4-Chloro-*N*-[3-[3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazin-1-ylcarbonyl]phenyl]benzamide



C27 H26 Cl N3 O4; Mol wt: 491.9724

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor, potentially useful in the treatment of allergic disorders, asthma, chronic bronchitis, atopic dermatitis, psoriasis, rheumatoid arthritis, multiple sclerosis, Crohn's disease, etc. Other specifically claimed aryl alkanoylpyridazine derivatives are:



Compound	R1	R2	Formula
284602	H	OC5H11	C ₃₂ H ₃₇ N ₃ O ₅
284603	H	OMe	C ₂₈ H ₂₉ N ₃ O ₅
284605	Cl	H	C ₂₇ H ₂₆ ClN ₃ O ₄

SOURCE – Merck KGaA.

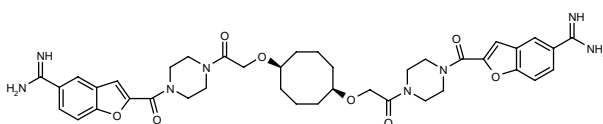
REFERENCES

1. Jonas, R. et al. (Merck Patent GmbH) *Aryl alkanoylpyridazines*. DE 19826841, WO 9965880.

AY-0068*

275939

2,2'-(*cis*-Cyclooctane-1,5-diylidioxy)bis(1-oxo-2,1-ethanediy)bis(piperazine-1,4-diyl)bis(carbonyl)bis(benzofuran-5-carboxamide)



C40 H48 N8 O8; Mol wt: 768.8672

ACTION – Potent and selective, nonpeptide tryptase inhibitor with respective K_i values for tryptase and thrombin of 0.029 nM and 150 μ M. It exhibited good metabolic stability when administered i.v. to rats and was able to dose-dependently inhibit passive cutaneous anaphylaxis (PCA) in rats when given at doses of 0.1-1 mg/kg i.v. 1 h prior to antigen challenge (51% inhibition at 1 mg/kg); compound had no effect against histamine-induced vascular permeability in rats. Potentially useful for the treatment of allergic and inflammatory conditions including bronchial asthma.

SOURCE – Yoshitomi (Welfide).

REFERENCES

1. Ono, S. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Tryptase inhibitor*. WO 9912918.

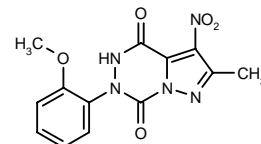
2. Ono, S. et al. *Syntheses and evaluation of amidinobenzofuran derivatives as tryptase inhibitors*. Bioorg Med Chem Lett 1999, 9(23): 3285.

*Identified compound **275939** (see **275935**) Drug Data Rep 1999, 021(08): 0689.

TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES (COPD)

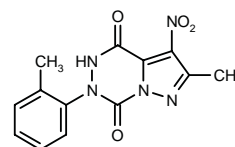
284074

2-Methyl-6-(2-methoxyphenyl)-3-nitro-4,5,6,7-tetrahydropyrazolo[1,5-*d*][1,2,4]triazine-4,7-dione



C13 H11 N5 O5; Mol wt: 317.2599

ACTION – Potent human leukocyte elastase (HLE) inhibitor proven to significantly suppress HLE-induced pulmonary injury in rats (50% inhibition at 100 mg/kg p.o. 3 h prior to HLE). Potentially useful for the treatment of pulmonary emphysema, cystic fibrosis, acute respiratory distress syndrome, bronchial secretory cell metaplasia and rheumatoid arthritis. Another related compound is:



284075: C13 H11 N5 O4

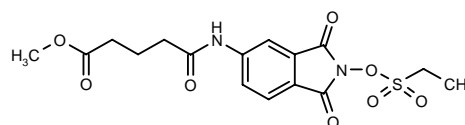
SOURCE – Università di Ferrara, Ferrara (IT).

REFERENCES

1. Baraldi, P.G. et al. *1H-Pyrazolo[2,3-*d*][1,2,4]triazine-3,7-diones as a new class of human leukocyte elastase inhibitors*. Arzneim-Forsch Drug Res 1999, 49(12): 997.

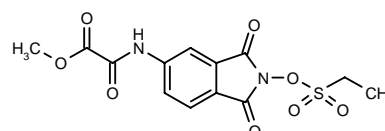
284568

5-[2-(Ethylsulfonyloxy)-1,3-dioxo-2,3-dihydro-1*H*-isindol-5-ylamino]-5-oxopentanoic acid methyl ester



C16 H18 N2 O8 S; Mol wt: 398.3902

ACTION – Potent human leukocyte elastase (HLE) inhibitor with 16-fold selectivity for HLE over chymotrypsin. Potentially useful for the treatment of chronic obstructive pulmonary disease. Another compound from this series of 6-acylamino-substituted-1*H*-isindole-1,3-diones is:



284569: C13 H12 N2 O8 S

SOURCES – State University of New Jersey, Piscataway, NJ (US); University of South Alabama, Mobile, AL (US).

REFERENCES

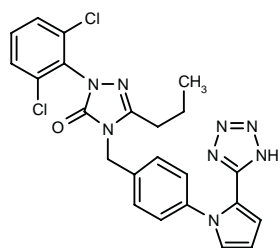
1. Kerrigan, J.E. et al. 6-Acylamino-2-[(alkylsulfonyl)oxy]-1H-isoindole-1,3-dione mechanism-based inhibitors of human leukocyte elastase. *Bioorg Med Chem Lett* 2000, 10(1): 27.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

283767

2-(2,6-Dichlorophenyl)-5-propyl-4-[4-[2-(1H-tetrazol-5-yl)-1H-pyrrol-1-yl]benzyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



C23 H20 Cl2 N8 O; Mol wt: 495.3720

ACTION – Nonpeptide angiotensin II AT₁ receptor antagonist, as demonstrated against ALL-mediated contractions in rabbit aorta, with potential in the treatment of hypertension.

SOURCE – China Pharmaceutical University, Nanjing (CN).

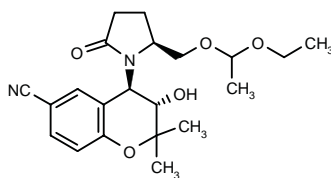
REFERENCES

1. Xu, J. et al. Synthesis and bioactivity of 1-aryl-3-alkyl-1,4-dihydro-4-substituted-5H-1,2,4-triazolinones-5. *J Chin Pharm Univ* 1999, 30(5): 323.

MJ-355

283568

trans-4-[2(S)-(1-Ethoxyethoxymethyl)-5-oxopyrrolidin-1-yl]-3-hydroxy-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-6-carbonitrile



C21 H28 N2 O5; Mol wt: 388.4612

M.p. 130-2 °C.

ACTION – ATP-sensitive potassium (K_{ATP}) channel opener proven to dose-dependently (0.005-0.1 mg/kg i.v.) decrease mean arterial blood pressure in spontaneously hypertensive rats, starting at 10-15 min after administration and persisting for more than 3 h; this effect was not accompanied by tachycardia and was reversed by the selective K_{ATP} channel blocker glibenclamide. In rats with myocardial ischemia-reperfusion injury induced by 45-min occlusion of the left coronary artery followed by 1 h of reperfusion, pretreatment with compound (0.02 mg/kg i.v.) significantly reduced the number of ventricular premature contractions and ventricular tachycardia, the duration of ventricular fibrillation, the mortality rate and the myocardial infarct size (20% reduction when given 5 min before reperfusion); all these effects of MJ-355 were reversed by glibenclamide pretreatment. Potentially useful for the treatment of hypertension and/or acute myocardial infarction.

SOURCE – National Taiwan University, Taipei (TW).

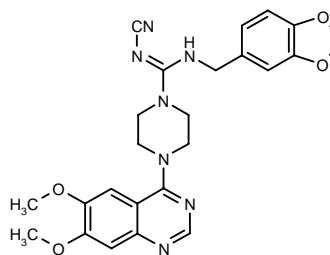
REFERENCES

1. Lee, Y.-M. et al. The effects of a newly synthesized ATP-sensitive potassium channel opener, MJ-355, on blood pressure and myocardial ischemia-reperfusion injury. *Jpn J Pharmacol* 1999, 81(2): 185.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

282901

N-(1,3-Benzodioxol-5-ylmethyl)-*N'*-cyano-4-(6,7-dimethoxyquinazolin-4-yl)piperazine-1-carboxamide



C24 H25 N7 O4; Mol wt: 475.5065

ACTION – Agent for the treatment of proliferative disorders such as arteriosclerosis, restenosis, cancer and glomerulonephritis that acts by inhibiting the phosphorylation of platelet-derived growth factor (PDGF) receptor (IC₅₀ = 0.19 μM in CHO cells expressing the human β-PDGF receptor). Within this series of heterocyclic compounds, the following are also included:

SOURCES – State University of New Jersey, Piscataway, NJ (US); University of South Alabama, Mobile, AL (US).

REFERENCES

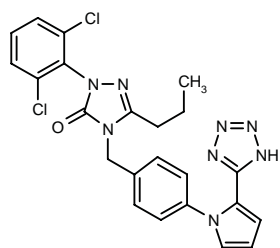
1. Kerrigan, J.E. et al. 6-Acylamino-2-[(alkylsulfonyl)oxy]-1H-isoindole-1,3-dione mechanism-based inhibitors of human leukocyte elastase. *Bioorg Med Chem Lett* 2000, 10(1): 27.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

283767

2-(2,6-Dichlorophenyl)-5-propyl-4-[4-[2-(1H-tetrazol-5-yl)-1H-pyrrol-1-yl]benzyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



C23 H20 Cl2 N8 O; Mol wt: 495.3720

ACTION – Nonpeptide angiotensin II AT₁ receptor antagonist, as demonstrated against ALL-mediated contractions in rabbit aorta, with potential in the treatment of hypertension.

SOURCE – China Pharmaceutical University, Nanjing (CN).

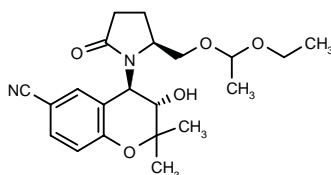
REFERENCES

1. Xu, J. et al. Synthesis and bioactivity of 1-aryl-3-alkyl-1,4-dihydro-4-substituted-5H-1,2,4-triazolinones-5. *J Chin Pharm Univ* 1999, 30(5): 323.

MJ-355

283568

trans-4-[2(S)-(1-Ethoxyethoxymethyl)-5-oxopyrrolidin-1-yl]-3-hydroxy-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-6-carbonitrile



C21 H28 N2 O5; Mol wt: 388.4612

M.p. 130-2 °C.

ACTION – ATP-sensitive potassium (K_{ATP}) channel opener proven to dose-dependently (0.005-0.1 mg/kg i.v.) decrease mean arterial blood pressure in spontaneously hypertensive rats, starting at 10-15 min after administration and persisting for more than 3 h; this effect was not accompanied by tachycardia and was reversed by the selective K_{ATP} channel blocker glibenclamide. In rats with myocardial ischemia-reperfusion injury induced by 45-min occlusion of the left coronary artery followed by 1 h of reperfusion, pretreatment with compound (0.02 mg/kg i.v.) significantly reduced the number of ventricular premature contractions and ventricular tachycardia, the duration of ventricular fibrillation, the mortality rate and the myocardial infarct size (20% reduction when given 5 min before reperfusion); all these effects of MJ-355 were reversed by glibenclamide pretreatment. Potentially useful for the treatment of hypertension and/or acute myocardial infarction.

SOURCE – National Taiwan University, Taipei (TW).

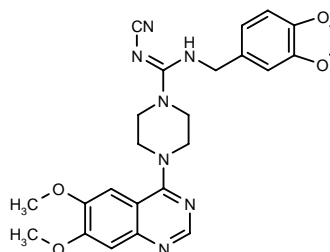
REFERENCES

1. Lee, Y.-M. et al. The effects of a newly synthesized ATP-sensitive potassium channel opener, MJ-355, on blood pressure and myocardial ischemia-reperfusion injury. *Jpn J Pharmacol* 1999, 81(2): 185.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

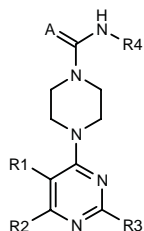
282901

N-(1,3-Benzodioxol-5-ylmethyl)-*N'*-cyano-4-(6,7-dimethoxyquinazolin-4-yl)piperazine-1-carboxamide



C24 H25 N7 O4; Mol wt: 475.5065

ACTION – Agent for the treatment of proliferative disorders such as arteriosclerosis, restenosis, cancer and glomerulonephritis that acts by inhibiting the phosphorylation of platelet-derived growth factor (PDGF) receptor (IC₅₀ = 0.19 μM in CHO cells expressing the human β-PDGF receptor). Within this series of heterocyclic compounds, the following are also included:



Compound	R1	R2	R3	R4	A	Formula
282902	-N=CHNH-		H	4-PhO-Ph	-O-	C ₂₂ H ₂₁ N ₇ O ₂
282903	-N=CHNH-		H	CH ₂ Ph	-S-	C ₁₇ H ₁₉ N ₇ S
282904	-N=CHNH-		NH ₂	4-PhO-Ph	-O-	C ₂₂ H ₂₂ N ₉ O ₂
282905	-CH=C(OMe)C(OMe)=CH-		H	4-Cl-PhCH ₂	N(CN)	C ₂₃ H ₂₄ ClN ₇ O ₂

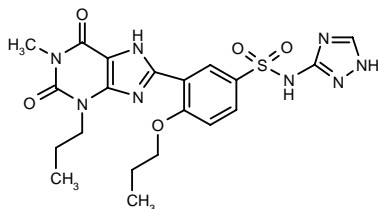
SOURCE – Kyowa Hakko.

REFERENCES

1. Matsuno, K. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Nitrogenous heterocyclic cpds.* WO 9951582.

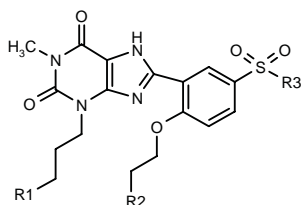
284131

3-(1-Methyl-3-propylxanthin-8-yl)-4-propoxy-N-(1H-1,2,4-triazol-3-yl)benzenesulfonamide



C₂₀ H₂₄ N₈ O₅ S; Mol wt: 488.5266

ACTION – Phosphodiesterase type 5 (PDE 5) inhibitor (IC₅₀ = 3 nM) with potential in the treatment of angina, hypertension, congestive heart failure, stroke, asthma, bronchitis, male erectile dysfunction, female sexual dysfunction, glaucoma and irritable bowel syndrome. Within this series of 8-phenylxanthine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
284132	Me	Me	4-Pyr-NH	C ₂₄ H ₂₈ N ₈ O ₅ S
284133	H	H	1,2,4-triazol-3-yl-NH	C ₁₉ H ₂₂ N ₈ O ₅ S
284135	H	Me	4-(NH ₂ CO)-1-Pip	C ₂₄ H ₃₂ N ₈ O ₆ S
284136	H	Me	1-Piz	C ₂₂ H ₃₀ N ₆ O ₅ S
284137	H	Me	4-Me-1-Piz	C ₂₃ H ₃₂ N ₆ O ₅ S
284138	H	Me	4-(CH ₂ CH ₂ OH)-1-Piz	C ₂₄ H ₃₄ N ₆ O ₆ S
284139	Me	Me	4-morpholinyl	C ₂₃ H ₃₁ N ₅ O ₆ S

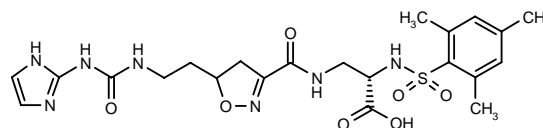
SOURCE – Almirall Prodesfarma.

REFERENCES

1. Vega Noverola, A. et al. (Almirall Prodesfarma, SA) *8-Phenylxanthine derivs. and their use as phosphodiesterase inhibitors.* WO 9962905.

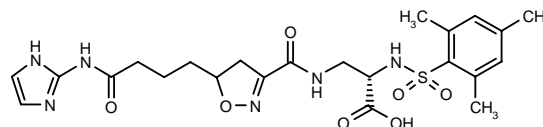
284562³

3-[5-[2-[3-(1H-Imidazol-2-yl)ureido]ethyl]-4,5-dihydro-isoxazol-3-ylcarboxamido]-2(S)-(2,4,6-trimethylphenyl)sulfonamido)propionic acid



C₂₂ H₂₉ N₇ O₇ S; Mol wt: 535.5791

ACTION – Integrin $\alpha_v\beta_3$ antagonist able to inhibit $\alpha_v\beta_3$ -mediated cell adhesion (IC₅₀ = 34 nM) with high selectivity relative to gpIIb/IIIa-mediated platelet aggregation (IC₅₀ = 120 μ M). Compound also strongly inhibited vitronectin-induced migration of $\alpha_v\beta_3$ -transfected HEK293 cells with an IC₅₀ of 140 nM. Potentially useful for the treatment of restenosis, osteoporosis, angiogenic ocular disorders and cancer. Another representative isoxazoline is:



284561:1-3 C₂₃ H₃₀ N₆ O₇ S

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Jadhav, P. et al. (DuPont Pharmaceuticals Co.) *Heterocyclic integrin inhibitor prodrugs.* WO 9843962.

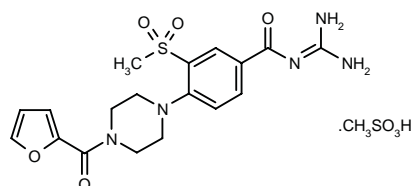
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3. Pitts, W.J. et al. *Isoxazolines as potent antagonists of the integrin $\alpha_v\beta_3$.* J Med Chem 2000, 43(1): 27.

BIIB-513*

254202

N²-[4-[4-(2-Furylcarbonyl)piperazin-1-yl]-3-(methylsulfonyl)benzoyl]guanidine methanesulfonate



C₁₈ H₂₁ N₅ O₅ S . C H₄ O₃ S; Mol wt: 515.5655

ACTION – Antiischemic and antiarrhythmic agent, an Na^+/H^+ exchange (NHE) inhibitor with an IC_{50} value of 27 nM for wild-type NHE-1 in HT-29 cells and high selectivity for NHE-1 over NHE-3 ($\text{IC}_{50} > 1000 \mu\text{M}$); it was also about 10-fold less active against recombinant human NHE-1 compared to wild-type enzyme. In a model of ischemia–reperfusion injury in dogs, compound (0.75 or 3.0 mg/kg by 15-min i.v. infusion) given 15 min prior to coronary artery occlusion (60 or 90 min) followed by reperfusion (3 h) produced significant reductions in infarct size and was more effective than ischemic preconditioning, which reduced infarct size only in the 60-min occlusion model. When compound was administered in combination with ischemic preconditioning, the reduction in infarct size obtained was greater than additive. Potentially useful as preventive therapy in patients at high risk for myocardial infarction.

SOURCE – Boehringer Ingelheim.

REFERENCES

1. Bürger, E. et al. (Boehringer Ingelheim GmbH) *Novel benzoyl guanidine derivs., process for their preparation and their use in the preparation of medicines*. DE 19601303, EP 0882031, WO 9726253.
2. Gumina, R.J. et al. *Antiarrhythmic and cardioprotective effect of Na^+/H^+ -exchange inhibition*. J Mol Cell Cardiol 1998, 30(7): Abstr 76.
3. Gumina, R.J. et al. *Direct comparison of the cardioprotective efficacy of ischemic preconditioning and Na^+/H^+ exchange inhibition*. Circulation 1998, 98(17, Suppl.): Abstr 1806.
4. Gumina, R.J. et al. *Inhibition of the Na^+/H^+ exchanger confers greater cardioprotection against 90 minutes of myocardial ischemia than ischemic preconditioning in dogs*. Circulation 1999, 100(25): 2519.
5. Gumina, R.J. et al. *Na^+/H^+ exchange inhibition and ischemic preconditioning synergize to decrease infarct size due to prolonged ischemia*. J Mol Cell Cardiol 1998, 30(7): Abstr 121.

*Identified compound **254202** Drug Data Rep 1997, 019(10): 0901.

CTGF-4

283933

Connective tissue growth factor-4

ACTION – Human protein that belongs to the CCN (connective tissue growth factor [CTGF], Cyr61/Cef10, neuroblastoma overexpressed gene [Nov]) family of proteins, cysteine-rich proteins with growth-regulatory functions. Polynucleotides encoding this protein, expression vectors, host cells, antibodies and recombinant methods for its production are also provided, as well as methods of diagnosing and treating connective tissue disorders such as atherosclerosis, cancer, arthritis, fibrosis and osteoporosis using this protein or agonists, antagonists or antibodies thereof.

SOURCE – Human Genome Sciences.

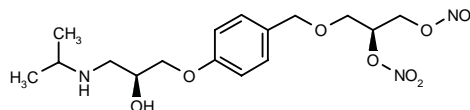
REFERENCES

1. Ruben, S.M. and Young, P.E. (Human Genome Sciences, Inc.) *Connective tissue growth factor-4*. WO 9962927.

PF-9404C

272823

1-[4-[2(*S*),3-Bis(nitrooxy)propoxymethyl]phenoxy]-3-(isopropylamino)propan-2(*S*)-ol



C16 H25 N3 O9; Mol wt: 403.3855

ACTION – Dual nitric oxide (NO) donor and β -adrenoceptor blocker proven to induce potent and long-lasting vasorelaxation in rat thoracic aorta strips ($\text{IC}_{50} = 33 \text{ nM}$), with a potency comparable to nitroglycerin ($\text{IC}_{50} = 49 \text{ nM}$), via a mechanism involving slow release of NO. Compound blocked the inotropic response to isoprenaline in guinea pig atria ($\text{IC}_{50} = 30 \text{ nM}$), with a potency comparable to *S*-propranolol ($\text{IC}_{50} = 22.4 \text{ nM}$) and superior to metoprolol and atenolol ($\text{IC}_{50} = 120$ and 192 nM , respectively). It displaced [^3H]-CGP-12177 binding from rat brain membranes with a K_i value of 7 nM , an affinity similar to *S*-propranolol ($K_i = 17 \text{ nM}$) but greater than metoprolol ($K_i = 170 \text{ nM}$) and atenolol ($K_i = 1200 \text{ nM}$), indicating cardiac β -blocking activity. Potentially useful for the treatment of ischemic heart injury, atherogenesis and hypertension.

SOURCE – Almirall Prodesfarma.

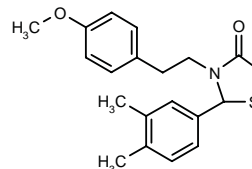
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3. *Company Profile: Almirall Prodesfarma*. DailyDrugNews.com (Daily Essentials) 1999, Feb 26.

ANTIARRHYTHMIC DRUGS

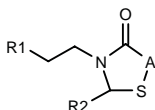
284350

3-[2-(4-Methoxyphenyl)ethyl]-2-(3,4-dimethylphenyl)-thiazolidin-4-one



C20 H23 N O2 S; Mol wt: 341.4727

ACTION – Antiarrhythmic agent, an inhibitor of voltage-dependent potassium channel function, particularly I_{Kur} and Kv1.5 potassium channels, shown to inhibit potassium currents in CHO cells stably expressing the Kv1.5 potassium channel subunit and $^{86}Rb^+$ influx through Kv1.5 channels expressed in CHO cells with respective IC_{50} values of 0.2 and 0.9 μM . Other exemplified compounds from this series of thiazolidinone and metathiazanone compounds include the following:



Compound	R1	R2	A	Formula
284351	4-MeO-Ph	3-MeO-Ph	-CH2-	$C_{19}H_{21}NO_3S$
284352	4-MeO-Ph	3,4-(Me)2-Ph	-(CH2)2-	$C_{21}H_{25}NO_2S$
284353	4-MeO-Ph	1,3-benzodioxol-4-yl	-(CH2)2-	$C_{20}H_{21}NO_4S$
284354	CH2CH2Ph	3,4-(Me)2-Ph	-CH2-	$C_{21}H_{25}NOS$
284355	4-MeO-Ph	5-Et-2-thienyl	-CH2-	$C_{18}H_{21}NO_2S_2$

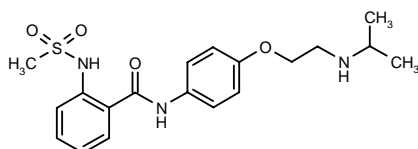
SOURCES – ICAGEN; Lilly.

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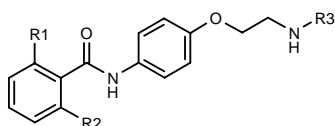
284771

N-[4-[2-(Isopropylamino)ethoxy]phenyl]-2-(methylsulfonamido)benzamide



$C_{19}H_{25}N_3O_4S$; Mol wt: 391.4895

ACTION – Antiarrhythmic agent especially for the treatment of atrial arrhythmia, reported to have increased safety compared to current drugs and to be devoid of ventricular function-suppressing and proarrhythmic effects. Antiarrhythmic activity was demonstrated by suppression of aconitine-induced atrial fibrillation in anesthetized dogs at 0.3 mg/kg i.v. Absence of ventricular effects was demonstrated in the dog Purkinje fiber assay, where it produced less than 10% change in action potential at 30 μM . No mortality was observed in mice following administration of 50 mg/kg i.v. Other compounds from this series of anilide derivatives include the following:



Compound	R1	R2	R3	Formula
284772	NHSO2Me	H	t-Bu	$C_{20}H_{27}N_3O_4S$
284776	OMe	OMe	cyclohexyl	$C_{23}H_{30}N_2O_4$

SOURCE – Mitsui Chemicals.

REFERENCES

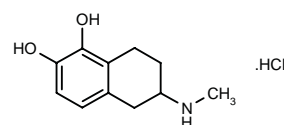
1. Yamashita, H. et al. (Mitsui Chemicals, Inc.) *Anilide derivs. and antiarrhythmic agents containing the same*. CA 2276719, EP 0968999.

HEART FAILURE THERAPY

CHF-1024

280569

6-(Methylamino)-5,6,7,8-tetrahydronaphthalene-1,2-diol hydrochloride



$C_{11}H_{15}NO_2 \cdot HCl$; Mol wt: 229.7054

ACTION – Prejunctional dopamine D_2 receptor and α_2 -adrenoceptor agonist able to reduce presynaptic norepinephrine release. In rats with left ventricular dysfunction following coronary artery occlusion, compound infused i.v. for 1 month at a dose of 0.33 mg/kg/day in combination with delapril (6 mg/kg/day in drinking water) reduced heart rate, NE excretion and myocardial interstitial collagen deposition and restored left ventricular cavity apical shape, with little or no hemodynamic effects. Potentially useful for the treatment of congestive heart failure.

SOURCES – Chiesi; Istituto di Richerche Farmacologiche Mario Negri, Milano (IT).

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2. Chiesi, P. et al. (Chiesi Farmaceutici SpA) *A process for the preparation of 5,6-dihydroxy-2-amino-1,2,3,4-tetrahydronaphthalene derivs.* WO 9529147.

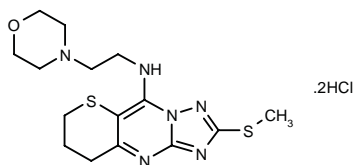
3. Latini, R. et al. *Comparative efficacy of a DA_2/α_2 agonist and a β -blocker in reducing adrenergic drive and cardiac fibrosis in an experimental model of left ventricular dysfunction after coronary artery occlusion*. J Cardiovasc Pharmacol 1998, 31(4): 601.

4. Masson, S. et al. *Effects of a DA_2/α_2 agonist and a β_1 -blocker in combination with an ACE inhibitor on adrenergic activity and left ventricular remodeling in an experimental model of left ventricular dysfunction after coronary artery occlusion*. J Cardiovasc Pharmacol 1999, 34(3): 321.

EGIS-9377

283473

2-(Methylsulfanyl)-N-[2-(4-morpholinyl)ethyl]-8,9-dihydro-7H-thiopyrano[3,2-d][1,2,4]triazolo[1,5-a]pyrimidin-5-amine dihydrochloride



C15 H22 N6 O S2 . 2HCl; Mol wt: 439.4336

ACTION – Cardiotonic agent with positive inotropic potency and efficacy similar to pimobendan in electrically paced guinea pig papillary muscle ($EC_{20} = 54$ and $92 \mu M$, respectively; 36 and 31% of the maximum effect of isoprenaline, respectively); in spontaneously beating guinea pig right atria, compound showed a negative chronotropic action ($EC_{50} = 14 \mu M$), in contrast to the positive chronotropic effect of pimobendan ($EC_{50} = 35 \mu M$). Its positive inotropic action may possibly be due to Ca^{2+} sensitization, as demonstrated by its ability to enhance Ca^{2+} -induced contractions in β -escin-skinned guinea pig trabecular muscles with a pCa_{50} value of 5.67. The negative chronotropic effect of compound may be due, at least in part, to prolongation of the action potential duration via inhibition of outward potassium currents.

SOURCE – Egis.

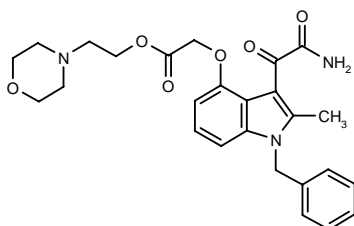
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2. Fukutomi, T. et al. Effects of pimobendan and EGIS-9377, cardiotonic agents, and OG-IV, a nucleoside mixture, administered during reperfusion after ischemia on stunned myocardium in dogs. Coron Artery Dis 2000, 11(1): 83.
3. Hattori, Y. et al. Cardiac profile of EGIS-9377, a novel cardiotonic agent as a Ca^{2+} sensitizer with bradycardiac activity. Naunyn-Schmied Arch Pharmacol 1999, 360(5): 585.

TREATMENT OF SHOCK

282774

2-[3-(Aminooxalyl)-1-benzyl-2-methyl-1H-indol-4-yl]oxy]acetic acid 2-(4-morpholinyl)ethyl ester



C26 H29 N3 O6; Mol wt: 479.5301

ACTION – Ester prodrug of a known inhibitor of human nonpancreatic secretory phospholipase A_2 ($sPLA_2$) with highly improved oral bioavailability as compared to previously described ester prodrugs thereof, as demonstrated in pharmacokinetic studies in rats and monkeys. Potentially useful in the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis, rheumatoid arthritis and the like.

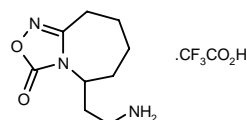
SOURCE – Lilly.

REFERENCES

1. Denney, M.L. et al. (Eli Lilly and Company) $sPLA_2$ inhibitor ester. WO 9956752.

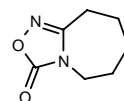
284508

5-(2-Aminoethyl)-6,7,8,9-tetrahydro-3H,5H-[1,2,4]-oxadiazolo[4,3-a]azepin-3-one trifluoroacetate



C9 H15 N3 O2 . C2 H F3 O2; Mol wt: 311.2584

ACTION – Nitric oxide synthase (NOS) inhibitor that preferentially inhibits the inducible isoform of the enzyme (iNOS) over the constitutive isoform, shown to reduce plasma nitrite levels in lipopolysaccharide-treated mice by 33 and 64% at doses of 3 and 10 mg/kg p.o., respectively. Potentially useful in the treatment of, among others, systemic hypotension associated with septic and/or toxic shock, autoimmune diseases and/or inflammatory bowel disease, congestive heart failure, atherosclerosis, migraine, irritable bowel syndrome, cerebral ischemia and stroke, as well as in conjunction with cytokine therapy and as an adjuvant to short-term immunosuppression in transplant therapy. Another exemplified compound from this series of bicyclic and tricyclic amidino derivatives is:



284509: C7 H10 N2 O2

SOURCE – Searle (Pharmacia).

REFERENCES

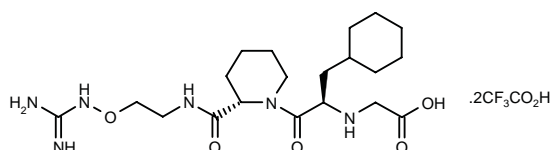
1. Hansen, D.W. Jr. et al. (G.D. Searle & Co.) Heterobicyclic and tricyclic nitric oxide synthase inhibitors. WO 9964426.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

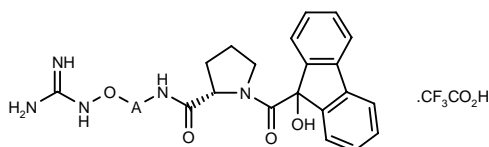
282633

N-[2-Cyclohexyl-1(*R*)-[2(*S*)-[*N*-[2-(guanidinooxy)ethyl]-carbamoyl]piperidin-1-ylcarbonyl]ethylglycine bis(trifluoroacetate)

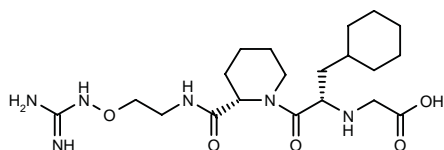


C₂₀ H₃₆ N₆ O₅ · 2 C₂ H₃ F₃ O₂; Mol wt: 668.5852

ACTION – Anticoagulant and antithrombotic agent with thrombin-inhibitory activity ($K_i = 20$ nM). Other exemplified compounds within this series of amino acid amidino-hydrazones, alkoxyguanidines and aminoguanidines include the following:



Compound	A	Formula
282635	-(CH ₂) ₂ -	C ₂₄ H ₂₆ F ₃ N ₅ O ₆
282636	-(CH ₂) ₃ -	C ₂₅ H ₂₈ F ₃ N ₅ O ₆



282634: C₂₀ H₃₆ N₆ O₅

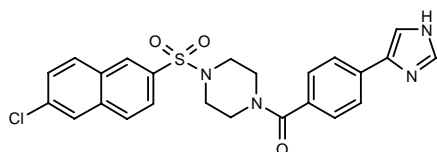
SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

1. Lu, T. et al. (3-Dimensional Pharmaceuticals, Inc.) *Amino acid amidino-hydrazones, alkoxyguanidines and aminoguanidines as protease inhibitors*. WO 9955355.

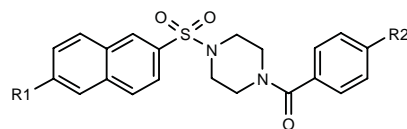
282777

1-[4-(6-Chloronaphthalen-2-ylsulfonyl)piperazin-1-yl]-1-[4-(1*H*-imidazol-4-yl)phenyl]methanone



C₂₄ H₂₁ Cl N₄ O₃ S; Mol wt: 480.9739

ACTION – Anticoagulant and antithrombotic agent, a selective inhibitor of factor Xa. Other exemplified heterocyclic compounds include the following:



Compound	R1	R2	Formula
282778	Br	1-imidazolyl	C ₂₄ H ₂₁ BrN ₄ O ₃ S
282780	Br	2-Me-4-imidazolyl	C ₂₅ H ₂₃ BrN ₄ O ₃ S
282781	Br	2-NH ₂ -4-imidazolyl	C ₂₄ H ₂₂ BrN ₅ O ₃ S
282782	Cl	3-oxo-2,3-dihydro-6-pyridazinyl	C ₂₅ H ₂₁ ClN ₄ O ₄ S

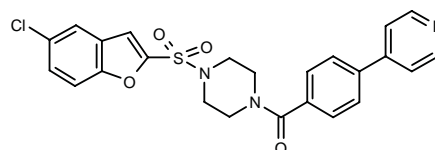
SOURCE – AstraZeneca.

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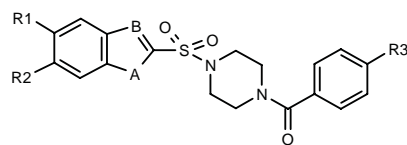
282807

1-[4-(5-Chlorobenzofuran-2-ylsulfonyl)piperazin-1-yl]-1-[4-(4-pyridinyl)phenyl]methanone



C₂₄ H₂₀ Cl N₃ O₄ S; Mol wt: 481.9580

ACTION – Anticoagulant and antithrombotic agent, a selective inhibitor of human factor Xa ($IC_{50} = 0.005$ μM). Other exemplified heterocyclic compounds include the following:



Compound	R1	R2	R3	A	B	Formula
282808	Cl	H	1-imidazolyl	O	CH	C ₂₂ H ₁₉ ClN ₄ O ₄ S
282809	Cl	H	4-Pyr	NH	CH	C ₂₄ H ₂₁ ClN ₄ O ₃ S
282810	Cl	H	4-pyrimidinyl	NH	CH	C ₂₃ H ₂₀ ClN ₅ O ₃ S
282811	Cl	H	4-pyridazinyl	NH	CH	C ₂₃ H ₂₀ ClN ₅ O ₃ S
282812	Cl	H	1-imidazolyl	NH	CH	C ₂₂ H ₂₀ ClN ₅ O ₃ S
282813	H	Cl	4-Pyr	NH	CH	C ₂₄ H ₂₁ ClN ₄ O ₃ S
282814	Cl	H	4-Pyr	NH	N	C ₂₃ H ₂₀ ClN ₅ O ₃ S
282815	Br	H	4-Pyr	NH	CH	C ₂₄ H ₂₁ BrN ₄ O ₃ S
282816	Cl	H	6-oxo-2,3-dihydro-3-pyridazinyl	NH	CH	C ₂₃ H ₂₀ ClN ₅ O ₄ S

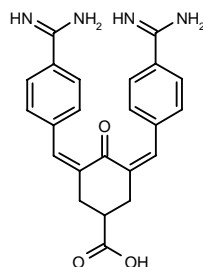
SOURCE – AstraZeneca.

REFERENCES

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284108

(Z,Z)-3,5-Bis(4-amidinobenzylidene)-4-oxocyclohexane-carboxylic acid



C23 H22 N4 O3; Mol wt: 402.4518

ACTION – Anticoagulant, a potent inhibitor of factor Xa ($K_i = 6.9$ nM) with high selectivity over other serine proteases including thrombin ($K_i > 50$ μ M) and trypsin ($K_i = 430$ nM).

SOURCE – Berlex.

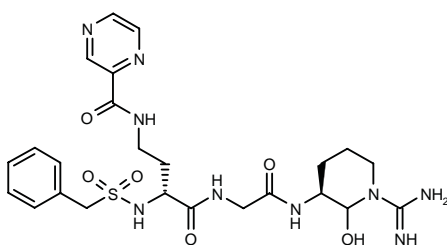
REFERENCES

1. Dallas, J.L. et al. (Berlex Laboratories, Inc.) (Z,Z), (Z,E) And (E,Z) isomers of substd. bis(phenylmethylene) cycloketones. US 5633381.

2. Guilford, W.J. et al. *Synthesis, characterization and structure-activity relationships of amidine-substituted (bis)benzylidene-cycloketone olefin isomers as potent and selective factor Xa inhibitors.* J Med Chem 1999, 42(26): 5415.

284399

N-[3(R)-[N-[N-[1-Amidino-2-hydroxypiperidin-3(S)-yl]-carbamoylmethyl]carbamoyl]-3-(benzylsulfonamido)prop-yl]pyrazine-2-carboxamide



C24 H33 N9 O6 S; Mol wt: 575.6477

ACTION – Anticoagulant, an inhibitor of factor Xa ($IC_{50} = 5$ nM) with high selectivity relative to other serine proteases including plasmin and thrombin ($IC_{50} = 521$ and > 2500 nM, respectively), and moderate selectivity relative to human trypsin ($IC_{50} = 166$ nM).

SOURCE – Corvas.

REFERENCES

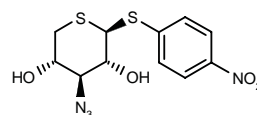
1. Ho, J.Z. et al. *Exploration solid-phase synthesis of factor Xa inhibitors: Discovery and application of P3-heterocyclic amides as novel types of non-basic arginine surrogates.* Bioorg Med Chem Lett 1999, 9(24): 3459.

GYKI-39484*,1,5-8

260202

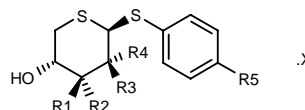
4-Nitrophenyl 3-azido-3-deoxy-1,5-dithio- β -D-xylopyranoside

RGH-1876



C11 H12 N4 O4 S2; Mol wt: 328.3718

ACTION – Potent, orally active antithrombotic agent, as demonstrated in various animal models of venous thrombosis although it had only weak anticoagulant effects even at doses as high as 100 mg/kg p.o. Elevation of the plasma levels of tissue factor pathway inhibitor (TFPI) has been suggested to contribute to its antithrombotic effect. Other representative thioglycosides include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
GYKI-39521 [266394]**,1,3,5-8 RGH-1875 262562 (as free base)	OH	H	H	OH	C(=NH)-SMe	HI	C ₁₃ H ₁₇ NO ₃ S ₃ ·HI
GYKI-39541 [266395] ^{2,4-8} RGH-1962	H	OH	OH	H	NO ₂		C ₁₁ H ₁₃ NO ₅ S ₂

SOURCES – Gedeon Richter; Institute for Drug Research.

REFERENCES

1. Kovácsné Bozó, E. et al. (Gedeon Richter Ltd.) *Novel anticoagulant glycosides and pharmaceutical compns. thereof.* EP 0907656, WO 9749716.

2. Kovácsné Bozó, E. et al. (Gedeon Richter Ltd.) *Novel anticoagulant glycosides and pharmaceutical compns. thereof.* WO 9928312.

3. Bozo, E. et al. *An economic synthesis of 1,2,3,4-tetra-O-acetyl-5-thio-D-xylopyranose and its transformation into 4-substituted-phenyl 1,5-dithio-D-xylopyranosides possessing antithrombotic activity.* Carbohydr Res 1998, 308(3-4): 297.

4. Bozo, E. et al. *Synthesis of 4-cyanophenyl and 4-nitrophenyl 1,5-dithio-L- and -D-arabinopyranosides possessing antithrombotic activity.* Carbohydr Res 1998, 311(4): 191.

5. Csomor, K. et al. *Comparative evaluation of new orally active thioglycosides on various thrombosis models.* Thromb Haemost 1999, (Suppl.): Abst 2133.

6. Csomor, K. et al. *Oral antithrombotic activity of new thioglycosides in rat models of venous thrombosis.* Haemostasis 1998, 28(Suppl. 2): Abst 463.

7. Szabó, G. et al. *Antithrombotic, anticoagulant effects and changes of TFPI level after per os administration of some new thioglycosides.* Thromb Haemost 1999, (Suppl.): Abst 2127.

8. Szabó, G. et al. *Thioglycoside antithrombotic agents.* Drugs Fut 1999, 24(11): 1241.

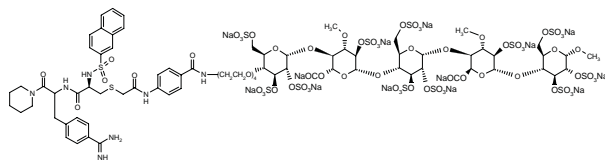
*Identified compound **260202** Drug Data Rep 1998, 020(05): 0405.

identified compound **262562 (see **260202**) Drug Data Rep 1998, 020(05): 0405.

NAPAP-PS

278865

4-[2-[2(*R*)-[*N*-[1-(4-Amidinobenzyl)-2-oxo-2-(1-piperidinylethyl)carbamoyl]-2-(2-naphthylsulfonamido)ethylsulfanyl]acetamido]-*N*-[11-(1-*O*-methyl-2,3,6-tri-*O*-sulfo- α -D-glucopyranosyl)(4 \rightarrow 1)(3-*O*-methyl-2-*O*-sulfo- α -L-idopyranosyluronic acid)(4 \rightarrow 1)(2,3,6-tri-*O*-sulfo- α -D-glucopyranosyl)(4 \rightarrow 1)(3-*O*-methyl-2-*O*-sulfo- β -D-glucopyranosyluronic acid)(4 \rightarrow 1)(2,3,6-tri-*O*-sulfo- α -D-glucopyranosyl-4-yloxy)]-3,6,9-trioxaundecyl]benzamide



C78 H96 N7 O70 S13 . 13 Na; Mol wt: 2967.3230

ACTION – Antithrombotic agent, a conjugate of heparin pentasaccharide with the active-site thrombin inhibitor NAPAP that acts as a potent thrombin inhibitor ($IC_{50} = 0.35 \mu M$) and promotes inhibition of factor Xa via stimulation of antithrombin III (ATIII) activity. The conjugate showed higher aqueous solubility and a significantly prolonged elimination half-life compared to NAPAP ($t_{1/2}$ approximately 90 and 9 min, respectively).

SOURCES – Leiden University, Leiden (NL); Organon.

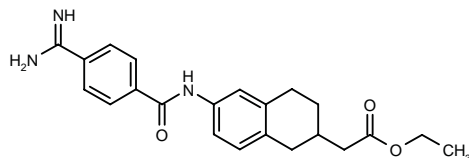
REFERENCES

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2. Buijsman, R.C. et al. *Design and synthesis of a novel synthetic NAPAP-pentasaccharide conjugate displaying a dual antithrombotic action.* Bioorg Med Chem Lett 1999, 9(14): 2013.

ANTIPLATELET THERAPY

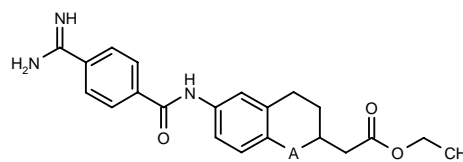
283269¹⁻³

2-[6-(4-Amidinobenzamido)-1,2,3,4-tetrahydro-2-naphthalenyl]acetic acid ethyl ester



C22 H25 N3 O3; Mol wt: 379.4575

ACTION – Ethyl ester prodrug of a known fibrinogen receptor antagonist* with a good pharmacokinetic profile in rats and guinea pigs after oral administration ($C_{max} = 5055$ and 1167 ng/ml, respectively, after 10 mg/kg p.o.) and an absolute oral bioavailability of 28% in rats. The active free acid inhibited fibrinogen binding to the gpIIb/IIIa receptor in human platelets with an IC_{50} value of 5 nM, exhibited high selectivity versus integrin $\alpha_v\beta_3$ receptors and potently inhibited ADP-induced human platelet aggregation ($IC_{50} = 0.19 \mu M$ or 67 ng/ml). Other prodrugs of known gpIIb/IIIa antagonists** include the following:



Compound	A	Formula
283270 ¹⁻³	CO	C ₂₂ H ₂₃ N ₃ O ₄
283271 ^{2,3}	O	C ₂₁ H ₂₃ N ₃ O ₄

SOURCE – Lilly.

REFERENCES

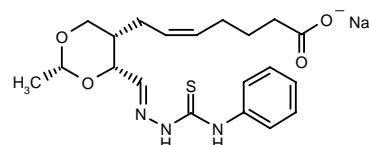
1. Fisher, M.J. et al. (Eli Lilly and Company) *Glycoprotein IIb/IIIa antagonists.* CA 2128348, EP 0635492, JP 1996188564, US 5618843.
2. Fisher, M.J. et al. (Eli Lilly and Company) *Glycoprotein IIb/IIIa antagonists.* EP 0804431, JP 1999502194, WO 9622288.
3. Fisher, M.J. et al. *Fused bicyclic Gly-Asp β -turn mimics with specific affinity for GPIIb-IIIa.* J Med Chem 1999, 42(23): 4875.

*See 222518 (see 219877) Drug Data Rep 1995, 017(06): 0538.

**See 222519 (see 219877) Drug Data Rep 1995, 017(06): 0538 and 239890 Drug Data Rep 1996, 018(10): 0903.

283925

7-[2(*R*)-Methyl-4(*R*)-[4-(phenyl)thiosemicarbazono-methyl]-1,3-dioxan-5(*S*)-yl]-5(*Z*)-heptenoic acid sodium salt



C20 H26 N3 Na O4 S; Mol wt: 427.4984

Pale yellow powder.

ACTION – Antiplatelet agent, a TxA_2 receptor antagonist ($IC_{50} = 77$ nM for displacement of [3H]-U-46619 binding from guinea pig platelets) proven to inhibit human platelet aggregation induced by collagen and U-46619 with respective IC_{50} values of 5 and 7.4 nM. Compound also inhibited monkey, dog, guinea pig and rat platelet aggregation induced by U-46619 or collagen ($IC_{50} = 5.6$ - 220 nM), as well as *ex vivo* guinea pig platelet aggregation (98.3 and 87.5% inhibition of U-46619- and collagen-induced aggregation, respectively, at 3.2 mg/kg p.o.). In a model of arachidonic acid-induced pulmonary infarction in mice, good efficacy was obtained at doses of 3.2 - 32 mg/kg p.o.

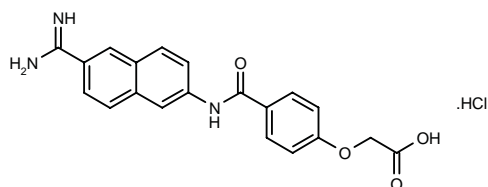
SOURCE – Fujisawa.

REFERENCES

1. Setoi, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Oxygen-containing heterocyclic cpd.* US 4929639.
2. Marusawa, H. et al. *Synthesis and biological activity of 4-methyl-3,5-dioxane derivatives as thromboxane A_2 receptor antagonists.* Bioorg Med Chem 1999, 7(11): 2635.

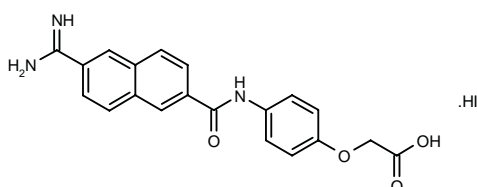
284175

2-[4-[N-(6-Amidino-2-naphthyl)carbamoyl]phenoxy]acetic acid hydrochloride



C₂₀ H₁₇ N₃ O₄ . HCl; Mol wt: 399.8322

ACTION – Antiplatelet agent, a potent fibrinogen (gpIIb/IIIa) receptor antagonist proven to inhibit ADP-induced human platelet aggregation with an IC₅₀ of 0.07 μM; it was practically inactive against a number of serine proteases including thrombin, factor Xa, plasmin and trypsin (K_i > 100 μM). Another chemically related compound from this series of naphthalene derivatives is:



284177: C₂₀ H₁₇ N₃ O₄ . HI

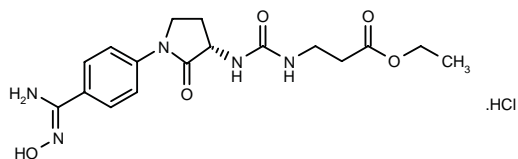
SOURCE – Yoshitomi (Welfide).

REFERENCES

1. Ashimori, A. et al. (The Green Cross Corporation) *Novel condensed-rings cpds. or their salts and their medicinal use.* JP 1995179407.
2. Ono, S. et al. *Preparation and pharmacological evaluation of novel glycoprotein (Gp) IIb/IIIa antagonists. 1. The selection of naphthalene derivatives.* Chem Pharm Bull 1999, 47(12): 1685.

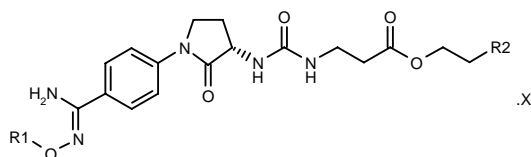
284356

3-[3-[1-[4-(N'-Hydroxyamidino)phenyl]-2-oxopyrrolidin-3(S)-yl]ureido]propionic acid ethyl ester hydrochloride



C₁₇ H₂₃ N₅ O₅ . HCl; Mol wt: 413.8596

ACTION – Double prodrug of the gpIIb/IIIa receptor antagonist SC-57101, the active free acid form of orbofiban⁺, proven to inhibit platelet aggregation *ex vivo* by 95% in dogs at 32 h after administration at a dose of 5 mg/kg p.o.; at this dose, compound resulted in significantly increased plasma levels of the parent carboxylic acid as compared to orbofiban at the same dose. Other compounds from this series of double prodrugs of gpIIb/IIIa receptor antagonists include the following:



Compound	R1	R2	R3	Formula
284358	H	Me	HCl	C ₁₈ H ₂₆ N ₅ O ₅ .HCl
284359	CON(Me)CH ₂ CH ₂ CH ₂ N(Me) ₂	H	2HCl	C ₂₄ H ₃₇ N ₇ O ₆ .2HCl

SOURCE – Searle (Pharmacia).

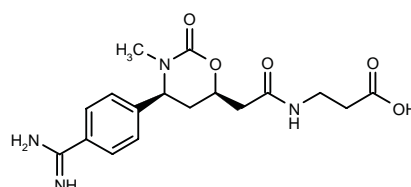
REFERENCES

1. Abood, N.A. et al. (G.D. Searle & Co.) *Double prodrugs of potent GPIIb/IIIa antagonists.* US 6025358, WO 9964397.

*Drug Data Rep 1997, 019(07): 0626.

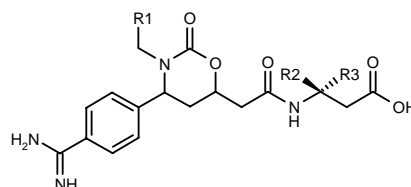
284727

3-[2-[4(S)-(4-Amidinophenyl)-3-methyl-2-oxoperhydro-1,3-oxazin-6(R)-yl]acetamido]propionic acid

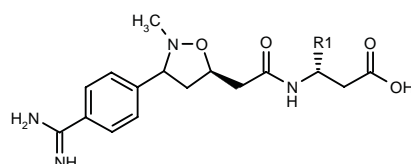


C₁₇ H₂₂ N₄ O₅; Mol wt: 362.3838

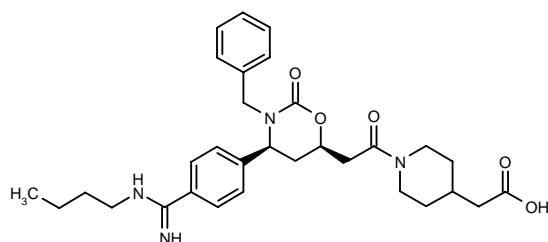
ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIIb/IIIa) receptor antagonist. Other specifically claimed compounds within this series of cyclic carbamates and isoxazolidines include the following:



Compound	R1	R2	R3	Isomer	Formula
284728	H	H	H	trans	C ₁₇ H ₂₂ N ₄ O ₅
284729	H	H	CH ₂ CH ₂ Ph	4S,6R	C ₂₅ H ₃₀ N ₄ O ₅
284730	H	3-Pyr	H	4S,6R	C ₂₂ H ₂₅ N ₅ O ₅
284731	H	Ph	H	4S,6R	C ₂₃ H ₂₆ N ₄ O ₅
284732	H	H	3-indolyl-CH ₂ CH ₂	4S,6R	C ₂₇ H ₃₁ N ₅ O ₅
284733	Ph	H	H	4R,6S	C ₂₃ H ₂₆ N ₄ O ₅



Compound	R1	Isomer	Formula
284735	H	S	C ₁₆ H ₂₂ N ₄ O ₄
284736	Me	R	C ₁₇ H ₂₄ N ₄ O ₄



284734: C31 H40 N4 O5

SOURCE – DuPont Pharmaceuticals.

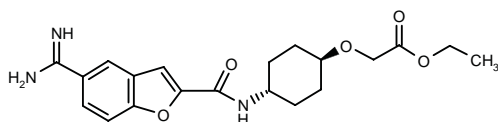
REFERENCES

1. Jin, F. and Confalone, P.N. (DuPont Pharmaceuticals Co.) *Cyclic carbamates and isoxazolidines as IIb/IIIa antagonists*. WO 0000481.

AR-0510*

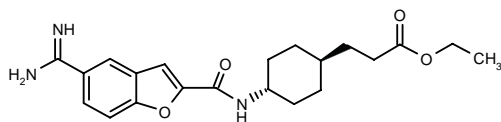
237380

trans-2-[4-(5-Amidino-1-benzofuran-2-ylcarboxamido)-cyclohexyloxy]acetic acid ethyl ester



C20 H25 N3 O5; Mol wt: 387.4390

ACTION – Antithrombotic agent, an ester prodrug of a potent and selective platelet gpIIb/IIIa receptor antagonist**, which inhibits ADP-induced human platelet aggregation with an IC₅₀ of 18 nM and is at least 1,000-fold more active in inhibiting platelet aggregation than human umbilical vein endothelial cell binding. The prodrug administered orally to dogs (10 mg/kg) produced 80% inhibition of platelet aggregation for 6 h and showed a good pharmacokinetic profile, with 15-18% oral bioavailability. Selected as a clinical candidate for development as an orally active antithrombotic agent. Another prodrug of a fibrinogen receptor antagonist*** is:



AR-0598 [284178]: C21 H27 N3 O4

SOURCE – Yoshitomi (Welfide).

REFERENCES

1. Ono, S. et al. (The Green Cross Corporation) *Novel fused-ring carboxylic acid cpds. or salt thereof, and medicinal use thereof*. EP 0712844, JP 1996053398, JP 1996231548, US 5635527, US 5753670, WO 9533720.

2. Ono, S. et al. *Preparation and pharmacological evaluation of novel glycoprotein (Gp) IIb/IIIa antagonists. 2. Condensed heterocyclic derivatives*. Chem Pharm Bull 1999, 47(12): 1694.

*Identified compound **237380** (see **231693**) Drug Data Rep 1996, 018(07): 0618.

See **237377 (see **231693**) Drug Data Rep 1996, 018(07): 0618.

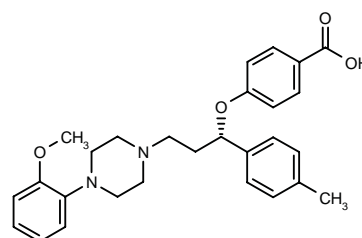
***See **231693** Drug Data Rep 1996, 018(07): 0618.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

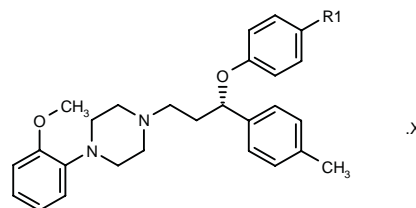
284870

4-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-(S)-(4-methylphenyl)propoxy]benzoic acid



C28 H32 N2 O4; Mol wt: 460.5708

ACTION – α_1 -Adrenoceptor antagonist shown to block phenylephrine-induced contractions in smooth muscle preparations from rabbit urethra and prostate with pA₂ values of 8.73 and 8.67, respectively. Potentially useful in the treatment or prevention of hypertension, congestive heart failure, myocardial ischemia, arrhythmia, angina pectoris and urinary disturbances and frequent urination associated with prostatic hypertrophy. Other exemplified compounds from this series of *N*-phenyl-*N'*-phenylpropylpiperazine derivatives include the following:

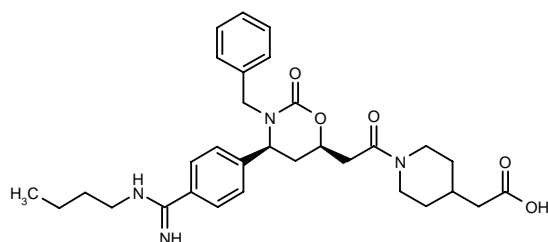


Compound	R1	X	Formula
284871	CN	2HCl	C ₂₈ H ₃₁ N ₃ O ₂ ·2HCl
284873	3-indolyl-CO	HCl	C ₃₆ H ₃₇ N ₃ O ₃ ·HCl

SOURCE – Zeria.

REFERENCES

1. Sato, H. et al. (Zeria Pharmaceutical Co., Ltd.) *N-Phenyl-N'-phenylpropylpiperazine derivs. and process for the preparation thereof*. WO 0000471.



284734: C31 H40 N4 O5

SOURCE – DuPont Pharmaceuticals.

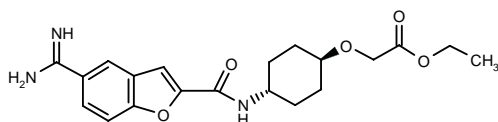
REFERENCES

1. Jin, F. and Confalone, P.N. (DuPont Pharmaceuticals Co.) *Cyclic carbamates and isoxazolidines as IIb/IIIa antagonists*. WO 0000481.

AR-0510*

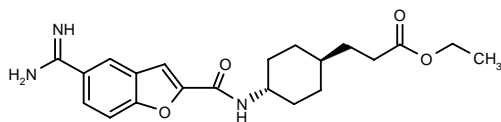
237380

trans-2-[4-(5-Amidino-1-benzofuran-2-ylcarboxamido)-cyclohexyloxy]acetic acid ethyl ester



C20 H25 N3 O5; Mol wt: 387.4390

ACTION – Antithrombotic agent, an ester prodrug of a potent and selective platelet gpIIb/IIIa receptor antagonist**, which inhibits ADP-induced human platelet aggregation with an IC_{50} of 18 nM and is at least 1,000-fold more active in inhibiting platelet aggregation than human umbilical vein endothelial cell binding. The prodrug administered orally to dogs (10 mg/kg) produced 80% inhibition of platelet aggregation for 6 h and showed a good pharmacokinetic profile, with 15-18% oral bioavailability. Selected as a clinical candidate for development as an orally active antithrombotic agent. Another prodrug of a fibrinogen receptor antagonist*** is:



AR-0598 [284178]: C21 H27 N3 O4

SOURCE – Yoshitomi (Welfide).

REFERENCES

1. Ono, S. et al. (The Green Cross Corporation) *Novel fused-ring carboxylic acid cpds. or salt thereof, and medicinal use thereof*. EP 0712844, JP 1996053398, JP 1996231548, US 5635527, US 5753670, WO 9533720.

2. Ono, S. et al. *Preparation and pharmacological evaluation of novel glycoprotein (Gp) IIb/IIIa antagonists. 2. Condensed heterocyclic derivatives*. Chem Pharm Bull 1999, 47(12): 1694.

*Identified compound **237380** (see **231693**) Drug Data Rep 1996, 018(07): 0618.

See **237377 (see **231693**) Drug Data Rep 1996, 018(07): 0618.

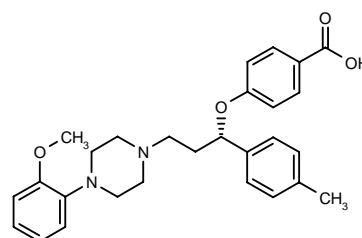
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RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

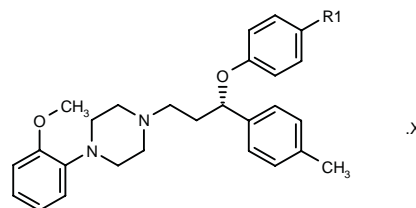
284870

4-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-(S)-(4-methylphenyl)propoxy]benzoic acid



C28 H32 N2 O4; Mol wt: 460.5708

ACTION – α_1 -Adrenoceptor antagonist shown to block phenylephrine-induced contractions in smooth muscle preparations from rabbit urethra and prostate with pA_2 values of 8.73 and 8.67, respectively. Potentially useful in the treatment or prevention of hypertension, congestive heart failure, myocardial ischemia, arrhythmia, angina pectoris and urinary disturbances and frequent urination associated with prostatic hypertrophy. Other exemplified compounds from this series of *N*-phenyl-*N'*-phenylpropylpiperazine derivatives include the following:



Compound	R1	X	Formula
284871	CN	2HCl	C ₂₈ H ₃₁ N ₃ O ₂ ·2HCl
284873	3-indolyl-CO	HCl	C ₃₆ H ₃₇ N ₃ O ₃ ·HCl

SOURCE – Zeria.

REFERENCES

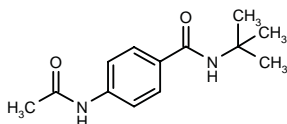
1. Sato, H. et al. (Zeria Pharmaceutical Co., Ltd.) *N-Phenyl-N'-phenylpropylpiperazine derivs. and process for the preparation thereof*. WO 0000471.

GASTROINTESTINAL DRUGS

INFLAMMATORY BOWEL DISEASE THERAPY

283852

4-Acetamido-*N*-(*tert*-butyl)benzamide



C₁₃ H₁₈ N₂ O₂; Mol wt: 234.2972

ACTION – Agent for the treatment or prevention of inflammatory bowel disease (IBD) reported to be able to mitigate the oxidative stress resulting from an inflammatory response. Compound was shown to be active in the TNBS-induced colonic inflammation model of IBD in rats following oral administration at 30 and 70 mg/kg, as well as in the dextran sulfate-induced IBD model in mice at 10-30 mg/kg p.o. In addition, it was shown to inhibit TNF- α -induced reactive oxygen species (ROS) in SK-N-MC cells at 100 μ M, to protect against TNF- α -induced apoptosis in human fetal brain cells at concentrations as low as 0.01 μ M and to inhibit TNF- α -induced reductions in BCL-2 in SK-N-MC cells at 100 μ M. Compound exhibited antiinflammatory activity in a rat adjuvant-induced arthritis model at 100 mg/kg p.o. A specifically claimed compound from a series of benzamide derivatives.

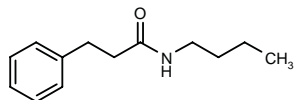
SOURCE – Centaur.

REFERENCES

1. Flitter, W.D. et al. (Centaur Pharmaceuticals, Inc.) *Benzamide therapeutics for the treatment of inflammatory bowel disease*. WO 9959569.

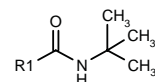
283853

N-Butyl-3-phenylpropionamide

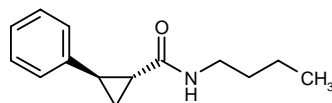


C₁₃ H₁₉ N O; Mol wt: 205.2991

ACTION – Agent for the treatment or prevention of inflammatory bowel disease, a representative compound from a series of amide derivatives, wherein the following are also specifically claimed:



Compound	R1	Formula
283855	4-CF ₃ -Ph	C ₁₂ H ₁₄ F ₃ NO
283856	2-OH-Ph	C ₁₁ H ₁₅ NO ₂
283857	2-Naph	C ₁₅ H ₁₇ NO
283858	5-indolyl	C ₁₃ H ₁₆ N ₂ O
283859	1-Ac-5-indolyl	C ₁₅ H ₁₈ N ₂ O ₂



283854: C₁₄ H₁₉ N O

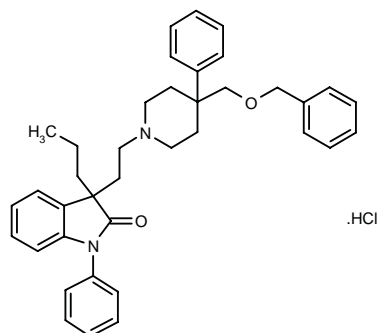
SOURCE – Centaur.

REFERENCES

1. Flitter, W.D. et al. (Centaur Pharmaceuticals, Inc.) *Amide therapeutics for the treatment of inflammatory bowel disease*. WO 9959582.

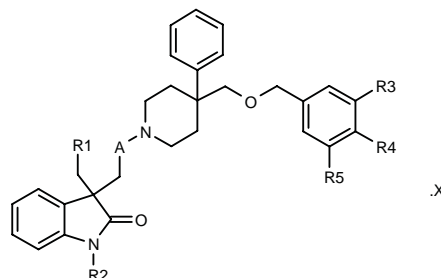
284160

3-[2-[4-(Benzyloxymethyl)-4-phenylpiperidin-1-yl]ethyl]-1-phenyl-3-propyl-2,3-dihydro-1*H*-indol-2-one hydrochloride



C₃₈ H₄₂ N₂ O₂ . HCl; Mol wt: 595.2227

ACTION – Neurokinin, particularly NK₁ and NK₂, receptor antagonist, potentially useful in the treatment of gastrointestinal inflammatory disorders such as Crohn's disease, inflammatory disorders such as psoriasis and rheumatoid arthritis, migraine, urinary disorders and CNS disorders. Other exemplified compounds from this series of oxindole derivatives include the following:



Compound	R1	R2	R3	R4	R5	A	X	Formula
284161	Et	H	CF ₃	H	CF ₃	-(CH ₂) ₃ -		C ₃₆ H ₄₀ F ₆ N ₂ O ₂
284162	i-Pr	H	CF ₃	H	CF ₃	-CH ₂ -		C ₃₅ H ₃₈ F ₆ N ₂ O ₂
284163	CH ₂ CH ₂ OH	H	CF ₃	H	CF ₃	-(CH ₂) ₃ -	HCl	C ₃₆ H ₄₀ F ₆ N ₂ O ₃ .HCl

Compound	R1	R2	R3	R4	R5	A	X	Formula
284164	CH ₂ CH ₂ CO ₂ Et	H	CF ₃	H	CF ₃	-(CH ₂) ₃ -	HCl	C ₃₅ H ₄₄ F ₆ N ₂ O ₄ .HCl
284165	CH ₂ CH ₂ CO ₂ H	H	CF ₃	H	CF ₃	-(CH ₂) ₃ -	HCl	C ₃₇ H ₄₀ F ₆ N ₂ O ₄ .HCl
284166	1-pyrrolidinyl- -COCH ₂ CH ₂	H	CF ₃	H	CF ₃	-(CH ₂) ₃ -	HCl	C ₄₁ H ₄₇ F ₆ N ₃ O ₃ .HCl
284167	CH ₂ CH ₂ CONH ₂	H	CF ₃	H	CF ₃	-(CH ₂) ₃ -		C ₃₇ H ₄₁ F ₆ N ₃ O ₃
284168	Et	Me	H	Cl	Cl	-CH ₂ -	HCl	C ₃₃ H ₃₈ Cl ₂ N ₂ O ₂ .HCl
284169	4-morpholinyl- -CH ₂	H	CF ₃	H	CF ₃	-(CH ₂) ₃ -	HCl	C ₃₉ H ₄₅ F ₆ N ₃ O ₃ .HCl
284170	CH ₂ CH ₂ - OSO ₂ Me	Me	CF ₃	H	CF ₃	-(CH ₂) ₃ -	HCl	C ₃₈ H ₄₄ F ₆ N ₂ O ₅ S.HCl

SOURCE – Sanofi-Synthélabo.

REFERENCES

- Gautier, C. et al. (Synthélabo) *Oxindole derivs. used as neurokinin receptor antagonists*. FR 2779429, WO 9962900.

AGENTS FOR CONSTIPATION

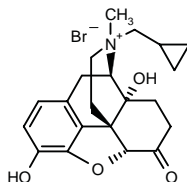
METHYLNALTREXONE BROMIDE

284766

17-(Cyclopropylmethyl)-4,5 α -epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanum bromide

N-Methylnaltrexone bromide

MRZ-2663BR



C₂₁ H₂₆ Br N O₄; Mol wt: 436.3434

ACTION – Peripheral opioid receptor antagonist that does not cross the blood–brain barrier in humans and is able to reverse the opioid effects mediated by peripheral receptors without interfering with pain relief. In preclinical animal models compound was able to block opioid-induced effects such as decrease in gastrointestinal transit, cough suppression and emesis, and in studies in opioid-tolerant primates no signs of withdrawal or reversal of opioid-induced analgesia were seen after treatment with compound. Rodents, but not humans, are able to demethylate a significant fraction of compound to naltrexone, which readily crosses into the CNS. Clinical trials have demonstrated its safety and efficacy in preventing opioid-induced constipation in normal volunteers and in patients on chronic opioid therapy.

SOURCES – University of Chicago, Chicago, IL (US); Mallinckrodt.

REFERENCES

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- Goldberg, L.I. (ARCH Development Corporation) *Method for reducing emesis and nausea induced by the administration of an emesis causing agent*. US 5102887.
- Goldberg, L.I. (University of Chicago) *Quaternary derivs. of noroxymorphone which relieve nausea and emesis*. US 4719215.
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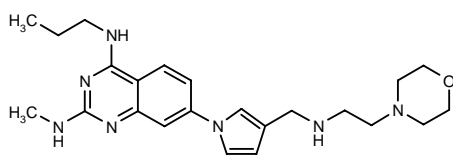
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TREATMENT OF DISORDERS OF GASTRIC EMPTYING

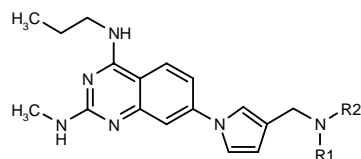
282857

*N*²-Methyl-7-[3-[2-(4-morpholinyl)ethylaminomethyl]-1*H*-pyrrol-1-yl]-*N*⁴-propylquinazoline-2,4-diamine



C₂₃ H₃₃ N₇ O; Mol wt: 423.5617

ACTION – Gastric prokinetic agent that exerts its action by virtue of its 5-HT₄ receptor-agonist activity, as demonstrated by the ability to relax carbachol-induced contractions of rat esophageal muscularis mucosae (EC₅₀ = 320 nM). *In vivo*, compound was shown to promote gastrointestinal motility in dogs at 0.1 mg/kg i.v. No mortality was observed following administration of 300 mg/kg p.o. to mice. Other exemplified compounds from this series of quinazoline derivatives include the following:



Compound	R1	R2	Formula
282858	-CH ₂ CH ₂ OCH ₂ CH ₂ -		C ₂₁ H ₂₈ N ₆ O
282859	-(CH ₂) ₄ -		C ₂₁ H ₂₈ N ₆
282860	2-Pyr-CH ₂	H	C ₂₃ H ₂₇ N ₇
282861	4-Pyr-CH ₂ CH ₂	H	C ₂₄ H ₂₉ N ₇
282862	2,6-(Me)2-4-morpholinyl-(CH ₂) ₃	H	C ₂₆ H ₃₉ N ₇ O
282863	1-Pip-COCH ₂	H	C ₂₄ H ₃₃ N ₇ O
282864	1-Et-2-pyrrolidinyl-CH ₂ NHCOCH ₂ CH ₂	H	C ₂₇ H ₄₀ N ₈ O
282865	4-morpholinyl-CO(CH ₂) ₅	H	C ₂₇ H ₃₉ N ₇ O ₂

SOURCE – Kyowa Hakko.

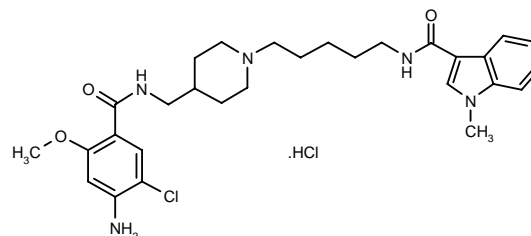
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Y-34959

286868

N-[5-[4-(4-Amino-5-chloro-2-methoxybenzamidoethyl)-piperidin-1-yl]pentyl]-1-methyl-1*H*-indole-3-carboxamide hydrochloride



C₂₉ H₃₈ Cl N₅ O₃ . HCl; Mol wt: 576.5651

ACTION – Potent 5-HT₄ receptor agonist (K_i = 0.3 nM) with high selectivity relative to other 5-HT receptors including 5-HT_{1A}, 5-HT₃ (IC₅₀ > 1 μM) and 5-HT₂ receptors (K_i = 110 nM), as well as dopamine D₂ receptors (IC₅₀ > 1 μM). Compound demonstrated agonist activity in functional studies in guinea pig ascending colon (EC₅₀ = 1.2 nM for inducing contractions). Studies in conscious dogs in the postprandial state demonstrated that it was able to rapidly enhance motility of both gastric antrum and ascending colon at a dose of 0.01 mg/kg i.v.; its effect on colon was blocked by azasetron, a selective 5-HT₃ receptor antagonist. Potentially useful as a stimulant of both upper and lower gastrointestinal motility.

SOURCE – Yoshitomi (Welfide).

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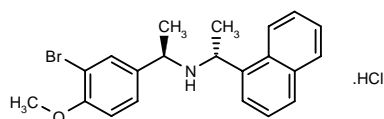
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ENDOCRINE DRUGS

THYROID DISEASE THERAPY

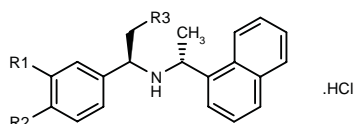
282520

N-[1(*R*)-(3-Bromo-4-methoxyphenyl)ethyl]-*N*-[1(*R*)-(1-naphthyl)ethyl]amine hydrochloride



C₂₁ H₂₂ Br N O . HCl; Mol wt: 420.7757

ACTION – Agent with the ability to modulate inorganic ion receptors and particularly cell-surface calcium receptors, giving an EC₅₀ value of 11 nM for increase in intracellular Ca²⁺ in HEK293 cells expressing the human parathyroid calcium receptor. Potentially useful in the treatment of primary or secondary hyperparathyroidism, Paget's disease, hypercalcemia of malignancy, osteoporosis, hypertension and renal osteodystrophy. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
282521	Me	OEt	H	C ₂₃ H ₂₇ NO.HCl
282522	H	I	H	C ₂₀ H ₂₀ IN.HCl
282523	Me	OMe	Me	C ₂₃ H ₂₇ NO.HCl

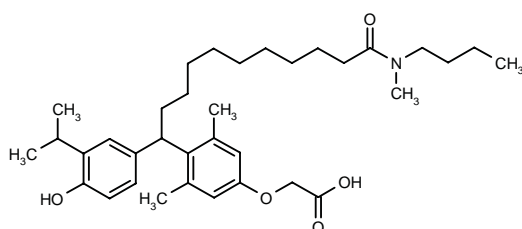
SOURCE – NPS Pharmaceuticals.

REFERENCES

1. Moe, S.T. et al. (NPS Pharmaceuticals, Inc.) *Inorganic ion receptor active cpds.* US 5981599.

284926

2-[4-[10-(*N*-Butyl-*N*-methylcarbamoyl)-1-(4-hydroxy-3-isopropylphenyl)decyl]-3,5-dimethylphenoxy]acetic acid



C₃₅ H₅₃ N O₅; Mol wt: 567.8057

ACTION – Thyroid hormone analogue that competes with [¹²⁵I]-T₃ for binding to human thyroid receptors hTR α and hTR β , giving K_d values of about 77 and 180 nM, respectively. Results from transactivation studies indicated that this compound acts as an antagonist at these receptors. Potentially useful for the treatment of hyperthyroidism or cardiac arrhythmias.

SOURCE – University of California, Oakland, Oakland, CA (US).

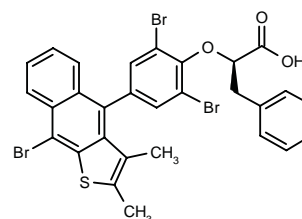
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ANTIDIABETIC DRUGS

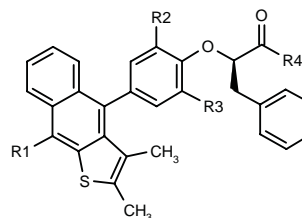
283768

2(*R*)-[2,6-Dibromo-4-(9-bromo-2,3-dimethylnaphtho-[2,3-*b*]thien-4-yl)phenoxy]-3-phenylpropionic acid



C₂₉ H₂₁ Br₃ O₃ S; Mol wt: 689.2599

ACTION – Agent for the treatment of metabolic disorders related to insulin resistance or hyperglycemia, a protein-tyrosine-phosphatase (PTPase) inhibitor (IC₅₀ = 0.115 μ M against recombinant PTP1B) proven to decrease blood glucose and insulin levels by 38.18 and 80.50%, respectively, in diabetic *ob/ob* mice at 25 mg/kg p.o. compared to decreases of 43 and 39%, respectively, for ciglitazone at 100 mg/kg p.o. Other compounds from this series of benzothiophene, benzofuran and indole derivatives are:



Compound	R1	R2	R3	R4	Formula
283769	Br	Me	Me	OH	C ₃₁ H ₂₇ BrO ₃ S
283770	SPh	Br	Br	OH	C ₃₅ H ₂₆ Br ₂ O ₃ S ₂
283772	Br	Br	Et	OH	C ₃₁ H ₂₆ Br ₂ O ₃ S
283775	Br	Et	Et	OH	C ₃₃ H ₃₁ BrO ₃ S
283776	Br	Me	Me	NHCH ₂ CO ₂ H	C ₃₃ H ₃₀ BrNO ₄ S

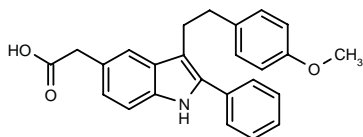
SOURCE – American Home Products.

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283983

3-[2-(4-Methoxyphenyl)ethyl]-2-phenyl-1*H*-indole-5-acetic acid



C25 H23 N O3; Mol wt: 385.4607

ACTION – Potent and subtype-selective peroxisome proliferator-activated receptor PPAR γ agonist ($pK_i = 7.3$; $pEC_{50} = 7.36$ in a transactivation assay in CV-1 cells) with potency similar to rosiglitazone ($pK_i = 7.33$; $pEC_{50} = 7.05$); compound at 10 μ M was devoid of affinity for or functional activity at PPAR α and PPAR δ subtype receptors. It showed an excellent pharmacokinetic profile in rats with a mean oral availability of 78 and 73%, respectively, after dosing as a solution or suspension. Considered a suitable candidate for development as an oral antihyperglycemic agent for the treatment of type II diabetes.

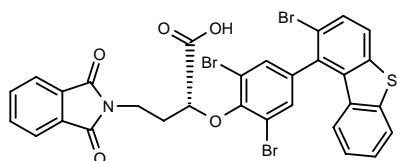
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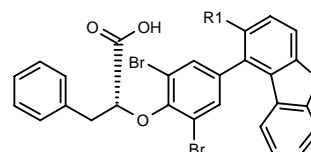
284143

2(*R*)-[2,6-Dibromo-4-(2-bromodibenzothien-1-yl)phenoxy]-4-phthalimidobutyric acid



C30 H18 Br3 N O5 S; Mol wt: 744.2522

ACTION – An inhibitor of protein-tyrosine-phosphatases (PTPases; $IC_{50} = 1.39 \mu$ M for inhibition of human recombinant PTP1B), potentially useful in the treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and vascular ischemic diseases. Other compounds from this series of 1-aryl-dibenzothiophenes include the following:



Compound	R1	Formula
284144	H	C ₂₇ H ₁₈ Br ₂ O ₃ S
284147	Br	C ₂₇ H ₁₇ Br ₃ O ₃ S

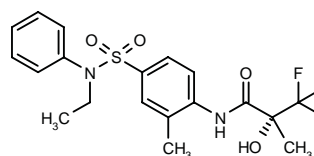
SOURCE – American Home Products.

REFERENCES

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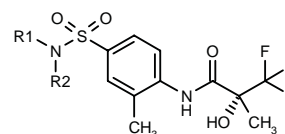
284201

N-[4-(*N*-Ethyl-*N*-phenylsulfamoyl)-2-methylphenyl]-3,3,3-trifluoro-2(*R*)-hydroxy-2-methylpropionamide



C19 H21 F3 N2 O4 S; Mol wt: 430.4449

ACTION – Agent for the treatment of diabetes mellitus, peripheral vascular disease, cardiac failure, myocardial ischemia, cerebral ischemia and reperfusion, muscle weakness, hyperlipidemia, atherosclerosis and Alzheimer's disease that acts by stimulating pyruvate dehydrogenase (PDH) activity. Other specifically claimed compounds from this series of benzenesulfonamide derivatives include the following:



Compound	R1	R2	Formula
284202	-CH2CH2OCH2CH2-		C ₁₅ H ₁₉ F ₃ N ₂ O ₅ S
284203	Me	Ph	C ₁₈ H ₁₉ F ₃ N ₂ O ₄ S
284204	Me	4-MeO-Ph	C ₁₉ H ₂₁ F ₃ N ₂ O ₅ S
284205	H	2-Cl-5-Me-Ph	C ₁₈ H ₁₈ ClF ₃ N ₂ O ₄ S

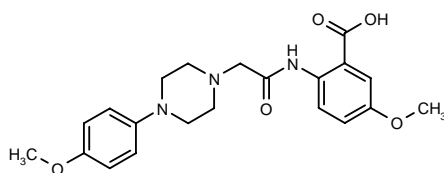
SOURCE – AstraZeneca.

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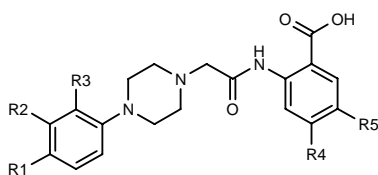
284329

5-Methoxy-2-[2-[4-(4-methoxyphenyl)piperazin-1-yl]acetamido]benzoic acid



C21 H25 N3 O5; Mol wt: 399.4445

ACTION – Antidiabetic agent particularly useful for the treatment of non-insulin-dependent diabetes, proven to reduce blood glucose levels in streptozotocin-diabetic rats by 20 and 31%, respectively, when given at 20 and 200 mg/kg/day p.o. x 4 days. Other compounds from this series of α -(1-piperazinyl)acetamido arenecarboxylic acid derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
284330	H	Cl	H	H	Cl	C ₁₉ H ₁₉ Cl ₂ N ₃ O ₃
284331	Cl	H	H	-OCH ₂ O-		C ₂₀ H ₂₀ ClN ₃ O ₅
284332	OMe	H	H	-OCH ₂ O-		C ₂₁ H ₂₃ N ₃ O ₆
284333	H	H	H	H	OMe	C ₂₀ H ₂₃ N ₃ O ₄
284334	Cl	H	H	H	OMe	C ₂₀ H ₂₂ ClN ₃ O ₄
284335	H	H	OMe	H	OMe	C ₂₁ H ₂₅ N ₃ O ₅
284336	H	OMe	H	H	OMe	C ₂₁ H ₂₅ N ₃ O ₅

SOURCE – Merck KGaA.

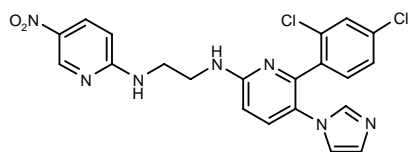
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284644

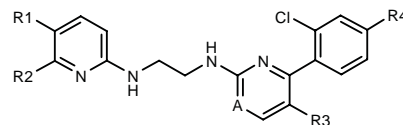
*N*¹-[6-(2,4-Dichlorophenyl)-5-(1*H*-imidazol-1-yl)pyridin-2-yl]-*N*²-(5-nitropyridin-2-yl)ethane-1,2-diamine

N-[6-(2,4-Dichlorophenyl)-5-(1*H*-imidazol-1-yl)pyridin-2-yl]-*N*-[2-(5-nitropyridin-2-ylamino)ethyl]amine



C21 H17 Cl2 N7 O2; Mol wt: 470.3183

ACTION – An inhibitor of glycogen synthase kinase 3 (GSK3) with potential in the treatment of GSK3-mediated disorders such as diabetes, Alzheimer's disease, obesity, atherosclerosis, hypertension, polycystic ovary syndrome, syndrome X, ischemia, traumatic brain injury, bipolar disorder, immunodeficiency and cancer. A representative compound from a series of pyrimidine and pyridine derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	A	Formula
284645	NO ₂	NH ₂	1-imidazolyl	Cl	CH	C ₂₁ H ₁₈ Cl ₂ N ₈ O ₂
284646	CN	H	1-imidazolyl	Cl	CH	C ₂₂ H ₁₇ Cl ₂ N ₇
284647	NO ₂	NH ₂	NO ₂	Cl	CH	C ₁₈ H ₁₅ Cl ₂ N ₇ O ₄
284649	NO ₂	NH ₂	4-Me-1-imidazolyl	Cl	CH	C ₂₂ H ₂₀ Cl ₂ N ₈ O ₂
284650	CN	H	4-Me-1-imidazolyl	Cl	CH	C ₂₃ H ₁₉ Cl ₂ N ₇
284651	NO ₂	H	2-imidazolyl	Br	N	C ₂₀ H ₁₆ BrClN ₈ O ₂

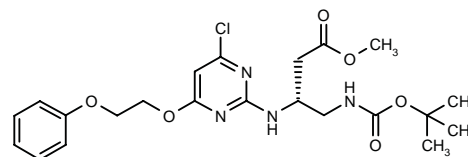
SOURCE – Chiron.

REFERENCES

1. Nuss, J.M. et al. (Chiron Corp.) *Inhibitors of glycogen synthase kinase 3*. WO 9965897.

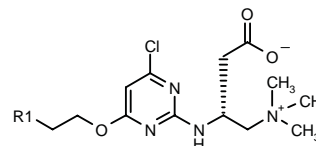
284812

4-(*tert*-Butoxycarbonylamino)-3(*R*)-[4-chloro-6-(2-phenoxyethoxy)pyrimidin-2-ylamino]butyric acid methyl ester

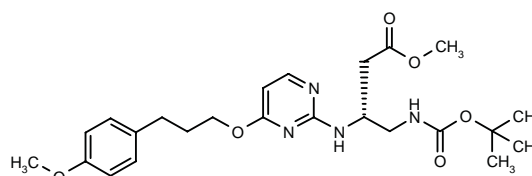


C22 H29 Cl N4 O6; Mol wt: 480.9461

ACTION – Hypoglycemic agent for the treatment of diabetes and diabetic complications, a carnitine-palmitoyl transferase (CPT) inhibitor (53.4% inhibition at 30 μ M). Other heterocyclic compounds include the following:



Compound	R1	Formula
284815	OPh	C ₁₉ H ₂₅ ClN ₄ O ₅
284817	4-MeO-PhCH ₂ CH ₂	C ₂₂ H ₃₁ ClN ₄ O ₄



284820: C24 H34 N4 O6

SOURCE – Nissan Chemical.

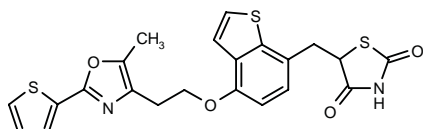
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BM-15.2054^{1,2}

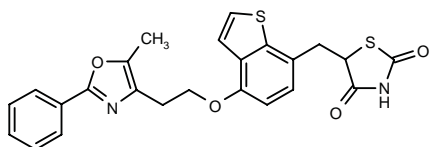
283576

5-[4-[2-[5-Methyl-2-(2-thienyl)oxazol-4-yl]ethoxy]-benzothien-7-ylmethyl]thiazolidine-2,4-dione



C22 H18 N2 O4 S3; Mol wt: 470.5922

ACTION – Potent thiazolidinedione insulin sensitizer proven to activate PPAR γ in transfection assays in CV-1 cells, with an effect superior to troglitazone and rosiglitazone. In insulin-resistant obese rats, chronic treatment (2 mg/day p.o. for 10 days) increased the stimulatory effect of insulin on muscle glycogen synthesis and significantly increased glucose oxidation in an insulin-independent manner. Acute *in vitro* exposure of muscle to compound significantly increased glucose uptake into muscle from both lean and obese rats independent of insulin stimulation, suggesting it may affect muscle glucose metabolism via other biochemical pathways. Potentially useful for the treatment of type II diabetes and obesity. Another related compound from this series of thiazolidinediones is:



BM-13.1258 [283575]¹⁻³: C24 H20 N2 O4 S2

SOURCE – Roche.

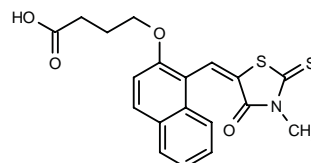
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TREATMENT OF DIABETIC COMPLICATIONS

284664

4-[1-(3-Methyl-4-oxo-2-thioxothiazolidin-5-ylidenemethyl)-naphthalen-2-yloxy]butyric acid



C19 H17 N O4 S2; Mol wt: 387.4783

M.p. 93-5 °C.

ACTION – Potent aldose reductase inhibitor (IC_{50} = 0.7 μ M against enzyme from rat crystalline lens) with superior *in vivo* activity compared to zenarestat in preventing sorbitol accumulation in sciatic nerve in streptozotocin-diabetic rats (34.6 and 21.8% inhibition, respectively, at 100 mg/kg p.o.). Selected for clinical development for the treatment of diabetic complications including neuropathy, retinopathy, nephropathy and cataract formation.

SOURCE – Dainippon Pharmaceutical.

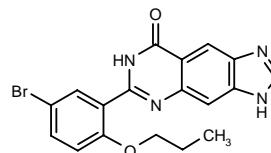
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TREATMENT OF MALE SEXUAL DYSFUNCTION

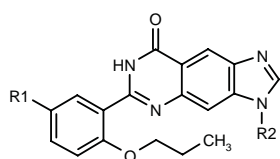
284422

6-(5-Bromo-2-propoxyphenyl)-7,8-dihydro-3H-imidazo[4,5-g]quinazolin-8-one

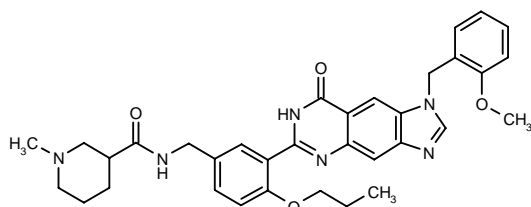


C18 H15 Br N4 O2; Mol wt: 399.2465

ACTION – Potent and selective inhibitor of phosphodiesterase type 5 (PDE5), potentially useful in the treatment of erectile dysfunction, cardiovascular disorders including hypertension, angina, heart failure, restenosis, atherosclerosis, myocardial infarction and peripheral vascular disease, as well as stroke, bronchitis, asthma, allergic rhinitis, glaucoma, gut motility disorders and certain forms of cancer. Other specifically claimed quinazolinone derivatives include the following:



Compound	R1	R2	Formula
284423	H	4-MeO-PhCH ₂	C ₂₆ H ₂₄ N ₄ O ₃
284424	1-Et-2-Piz-CO	H	C ₂₅ H ₂₈ N ₆ O ₃



284426: C₃₄ H₃₈ N₆ O₄

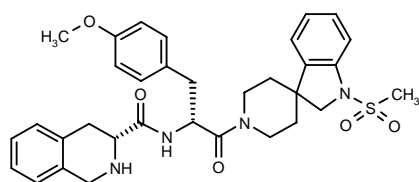
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Macor, J.E. et al. (Bristol-Myers Squibb Co.) *Quinazolinone inhibitors of cGMP phosphodiesterase*. WO 9964004.

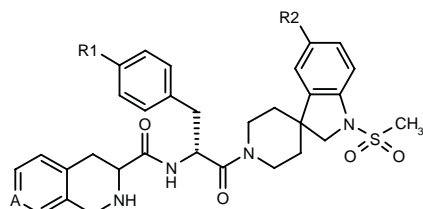
284477

N-[1(*R*)-[1-(Methanesulfonyl)spiro[2,3-dihydro-1*H*-indole-3,4'-piperidin]-1'-ylcarbonyl]-2-(4-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-3(*R*)-carboxamide

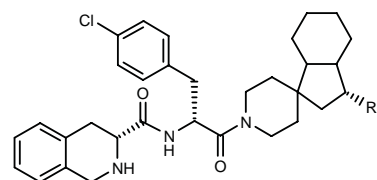


C₃₃ H₃₈ N₄ O₅ S; Mol wt: 602.7522

ACTION – Melanocortin receptor agonist with potential in the treatment of disorders responsive to the activation of melanocortin receptors such as obesity, diabetes and male and female sexual dysfunction. Other specifically claimed compounds from this series of spiro[2,3]-indole derivatives include the following:



Compound	R1	R2	A	Isomer	Formula
284478	Cl	F	C(OH)	S	C ₃₂ H ₃₄ ClFN ₄ O ₅ S
284479	Br	H	CH	R	C ₃₂ H ₃₆ BrN ₄ O ₄ S
284480	Cl	F	N	S	C ₃₁ H ₃₃ ClFN ₅ O ₄ S
284481	Cl	H	C(OCF ₃)	S	C ₃₃ H ₃₄ ClF ₃ N ₄ O ₅ S



Compound	R1	Formula
284482	CON(Me) ₂	C ₃₅ H ₄₅ ClN ₄ O ₃
284483	1,2,4-triazol-1-yl	C ₃₅ H ₄₃ ClN ₆ O ₂

SOURCE – Merck & Co.

REFERENCES

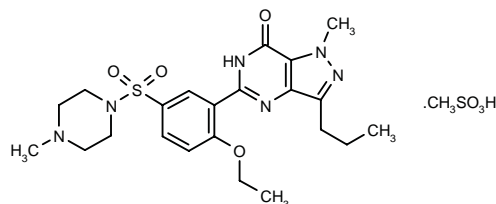
1. Nargund, R.P. et al. (Merck & Co., Inc.) *Spiropiperidine derivs. as melanocortin receptor agonists*. WO 9964002.

SILDENAFIL MESILATE

Prop INN

284741

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-methyl-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-one methanesulfonate



C₂₂ H₃₀ N₆ O₄ S . C H₄ O₃ S; Mol wt: 570.6886

ACTION – Novel salt of sildenafil* with unexpectedly high aqueous solubility, making it particularly suitable for use in aqueous intranasal formulations, which are reported to be associated with a more rapid absorption compared to the corresponding oral dose, resulting in a more rapid onset of action and efficacy at lower doses.

SOURCE – Pfizer.

REFERENCES

1. Billotte, A. et al. (Pfizer Ltd.) *Intranasal formulations for treating sexual disorders*. CA 2275554, EP 0967214.

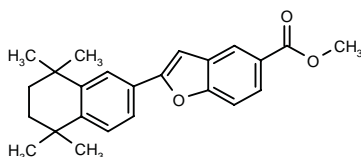
*Drug Data Rep 1998, 020(06): 0510.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

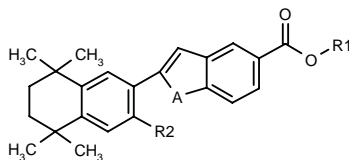
284172

2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)benzofuran-5-carboxylic acid methyl ester

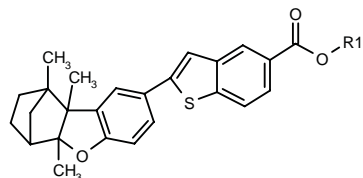


C24 H26 O3; Mol wt: 362.4664

ACTION – Agent for the treatment of skin disorders including psoriasis, acne, ichthyoses and other keratinization and hyperproliferative disorders with retinoic acid receptor (RAR)-modulating activity. Other compounds from this series of aromatic heterocyclic biaryl derivatives include the following:



Compound	R1	R2	A	Formula
284173	H	H	O	C ₂₃ H ₂₄ O ₃
284174	Me	H	S	C ₂₄ H ₂₆ O ₂ S
284176	H	H	S	C ₂₃ H ₂₄ O ₂ S
284181	Me	OMe	O	C ₂₅ H ₂₈ O ₄
284182	H	OMe	O	C ₂₄ H ₂₆ O ₄
284183	Me	OPr	O	C ₂₇ H ₃₂ O ₄
284184	H	OPr	O	C ₂₆ H ₃₀ O ₄
284185	Me	OC7H15	O	C ₃₁ H ₄₀ O ₄
284186	H	OC7H15	O	C ₃₀ H ₃₈ O ₄
284187	H	H	NH	C ₂₃ H ₂₅ NO ₂



Compound	R1	Formula
284179	Me	C ₂₆ H ₂₆ O ₃ S
284180	H	C ₂₅ H ₂₄ O ₃ S

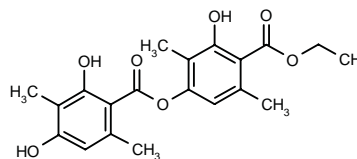
SOURCE – Galderma.

REFERENCES

- Charpentier, B. and Nedoncelle, P. (CIRD Galderma) *Biaryl heterocyclic aromatic cpds., pharmaceutical and cosmetic compns. containing them and uses*. CA 2274638, EP 0963981, FR 2779723, JP 2000026410.

284662

2,4-Dihydroxy-3,6-dimethylbenzoic acid 4-(ethoxycarbonyl)-3-hydroxy-2,5-dimethylphenyl ester



C20 H22 O7; Mol wt: 374.3868

ACTION – Potent nonredox inhibitor of LTB₄ biosynthesis (IC₅₀ = 0.8 μM in bovine polymorphonuclear lymphocytes) that displays antiproliferative activity against human keratinocyte HaCaT cells (IC₅₀ = 8.4 μM). Potentially useful for the treatment of inflammatory and hyperproliferative skin diseases such as psoriasis.

SOURCES – Universität Regensburg, Regensburg (DE); Westfälische Wilhelms-Universität, Münster (DE).

REFERENCES

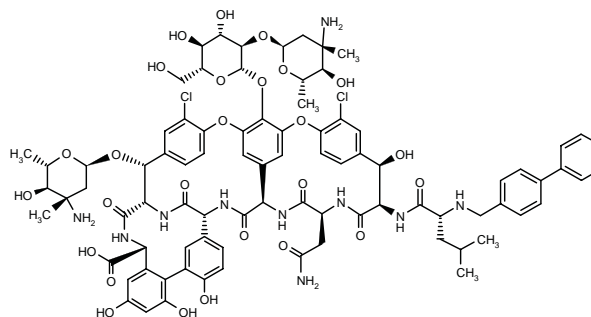
- Kumar, S. and Müller, K. *Depsides as non-redox inhibitors of leukotriene B₄ biosynthesis and HaCaT cell growth. 1. Novel analogues of barbatic and diffractaic acid*. Eur J Med Chem 1999, 34(12): 1035.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

282866

(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38*aR*)-22-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-*L*-glucopyranosyloxy)-44-[2-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-*L*-glucopyranosyl)-β-*D*-glucopyranosyloxy]-6-[*N*^α-(biphenyl-4-ylmethyl)-*D*-leucylamino]-3-(carbamoylmethyl)-10,19-dichloro-7,28,30,32-tetrahydroxy-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-1*H*,22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno[1,6,9]oxadiazacyclohexadecino-[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid



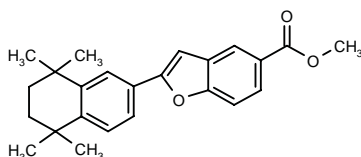
C85 H96 Cl2 N10 O26; Mol wt: 1744.6430

DERMATOLOGIC DRUGS

ANTIPSORIATICS

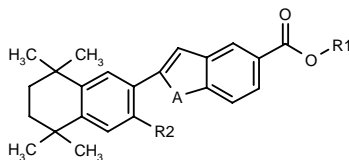
284172

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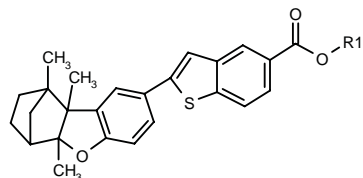


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Compound	R1	R2	A	Formula
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284176	H	H	S	C ₂₃ H ₂₄ O ₂ S
284181	Me	OMe	O	C ₂₅ H ₂₈ O ₄
284182	H	OMe	O	C ₂₄ H ₂₆ O ₄
284183	Me	OPr	O	C ₂₇ H ₃₂ O ₄
284184	H	OPr	O	C ₂₆ H ₃₀ O ₄
284185	Me	OC7H15	O	C ₃₁ H ₄₀ O ₄
284186	H	OC7H15	O	C ₃₀ H ₃₈ O ₄
284187	H	H	NH	C ₂₃ H ₂₅ NO ₂



Compound	R1	Formula
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284180	H	C ₂₅ H ₂₄ O ₃ S

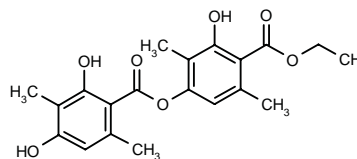
SOURCE – Galderma.

REFERENCES

1. Charpentier, B. and Nedoncelle, P. (CIRD Galderma) *Biaryl heterocyclic aromatic cpds., pharmaceutical and cosmetic compns. containing them and uses*. CA 2274638, EP 0963981, FR 2779723, JP 2000026410.

284662

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SOURCES – Universität Regensburg, Regensburg (DE); Westfälische Wilhelms-Universität, Münster (DE).

REFERENCES

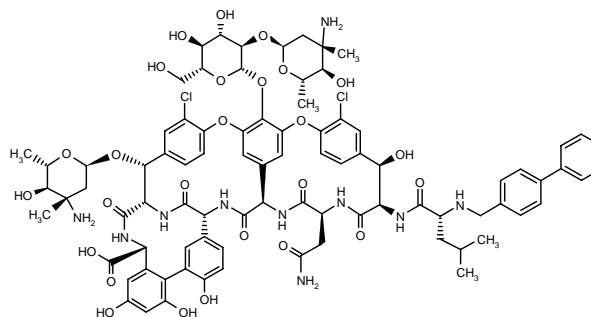
1. Kumar, S. and Müller, K. *Depsides as non-redox inhibitors of leukotriene B₄ biosynthesis and HaCaT cell growth. 1. Novel analogues of barbatic and diffractaic acid*. Eur J Med Chem 1999, 34(12): 1035.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

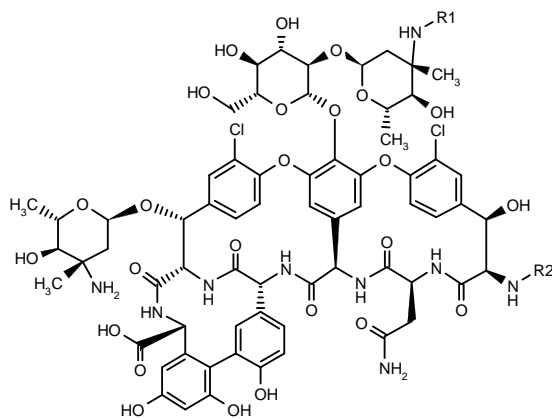
282866

(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38*aR*)-22-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-*L*-glucopyranosyloxy)-44-[2-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-*L*-glucopyranosyl)-β-*D*-glucopyranosyloxy]-6-[*N*^α-(biphenyl-4-ylmethyl)-*D*-leucylamino]-3-(carbamoylmethyl)-10,19-dichloro-7,28,30,32-tetrahydroxy-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38*a*-tetradecahydro-1*H*,22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno[1,6,9]oxadiazacyclohexadecino-[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid



C85 H96 Cl2 N10 O26; Mol wt: 1744.6430

ACTION – Antibacterial agent, a derivative of the known glycopeptide A-82846B reported to be useful especially against Gram-positive bacteria including methicillin-, vancomycin- and/or teicoplanin-resistant strains. Compound exhibited MIC values of 0.06 µg/ml or less, 0.06 µg/ml or less, 0.25 µg/ml, 0.06 µg/ml or less, 0.06 µg/ml or less, 64 µg/ml and > 64 µg/ml when tested against *Staphylococcus aureus* 1199A, *Staphylococcus haemolyticus* 105, *Staphylococcus epidermidis* 270, *Enterococcus faecium* 180-1, *Enterococcus gallinarum* 245, *Haemophilus influenzae* RD and *Escherichia coli* EC14, respectively. Other compounds from this series of N¹-modified glycopeptides include the following:



Compound	R1	R2	Formula
282867	4-(4-Cl-Ph)-PhCH ₂	i-BuCH ₂ CO	C ₈₅ H ₉₄ Cl ₃ N ₉ O ₂₆
282868	4-Ph-PhCH ₂	H-D-Pro-	C ₈₄ H ₉₂ Cl ₂ N ₁₀ O ₂₆
282869	4-Ph-PhCH ₂	H-D-Leu-	C ₈₅ H ₉₆ Cl ₂ N ₁₀ O ₂₆
282870	H	H-D-Leu-	C ₇₂ H ₈₆ Cl ₂ N ₁₀ O ₂₆
282871	4-Ph-PhCH ₂	H-D-Lys-	C ₈₅ H ₉₇ Cl ₂ N ₁₁ O ₂₆
282872	4-Ph-PhCH ₂	N-(t-BuOCO)-L-Pro-	C ₈₉ H ₁₀₀ Cl ₂ N ₁₀ O ₂₈
282873	C ₆ H ₁₃	N-(C ₆ H ₁₃)-d-Leu-	C ₈₄ H ₁₁₀ Cl ₂ N ₁₀ O ₂₆
282874	H	N-(C ₆ H ₁₃)-D-Leu-	C ₇₈ H ₉₈ Cl ₂ N ₁₀ O ₂₆

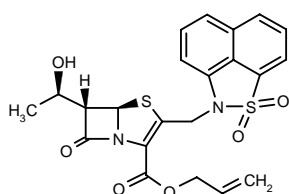
SOURCE – Lilly.

REFERENCES

1. Thompson, R.C. and Wilkie, S.C. (Eli Lilly and Company) *N1-Modified glycopeptides*. WO 9956760.

283745

(5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-(1,1-dioxonaphtho-[1,8-*cd*]isothiazol-2-ylmethyl)-2-penem-3-carboxylic acid allyl ester



C₂₂ H₂₀ N₂ O₆ S₂; Mol wt: 472.5400

ACTION – Carbapenem antibiotic with activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCNS). A representative compound from a series of penems substituted at the 2-position with a naphthosulfamylmethyl group.

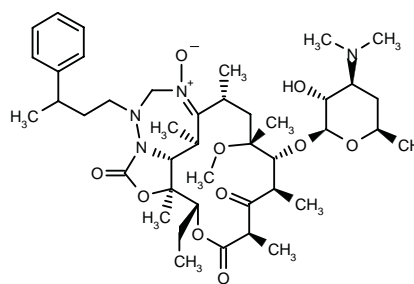
SOURCE – Merck & Co.

REFERENCES

1. Dininno, F.P. (Merck & Co., Inc.) *Naphthosulfamylmethyl penem antibacterials*. WO 9961448.

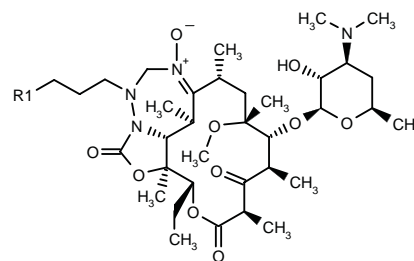
284117

9-Deoxy-11-deoxy-3-des(hexopyranosyloxy)-9-imino-6-*O*-methyl-3-oxo-11-(3-phenylbutylhydrazino)-9-*N*,11b-*N*-(methylene)erythromycin A 9-*N*-oxide 11a-*N*,12-*O*-cyclic carbamate



C₄₂ H₆₆ N₄ O₁₀; Mol wt: 787.0014

ACTION – A representative compound from a series of tricyclic 3-keto derivatives of 6-*O*-methylerythromycin with antibacterial and antiprotozoal activity, wherein the following are also included:



Compound	R1	Formula
284119	4-quinoliny	C ₄₄ H ₆₅ N ₅ O ₁₀
284120	4-Ph-1-imidazolyl	C ₄₄ H ₆₆ N ₆ O ₁₀
284121	2-MeO-Ph	C ₄₂ H ₆₆ N ₄ O ₁₁
284122	2-furyl	C ₃₉ H ₆₂ N ₄ O ₁₁
284123	1-benzimidazolyl	C ₄₂ H ₆₄ N ₆ O ₁₀
284124	1-indazolyl	C ₄₂ H ₆₄ N ₆ O ₁₀
284126	4-OH-Ph	C ₄₁ H ₆₄ N ₄ O ₁₁
284127	3-indolyl	C ₄₃ H ₆₅ N ₅ O ₁₀
284128	4-(3-Pyr)-1-imidazolyl	C ₄₃ H ₆₅ N ₇ O ₁₀

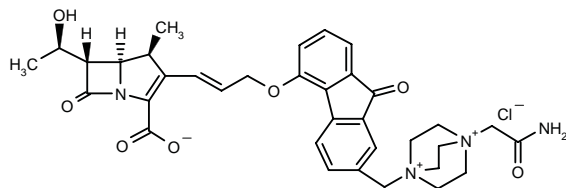
SOURCE – Pfizer.

REFERENCES

1. Wu, Y.-J. (Pfizer Products Inc.) *Tricyclic 3-keto derivs. of 6-O-methylerythromycin*. WO 9962920.

284199

(1*S*,5*R*,6*S*)-2-[3-[7-[4-(Carbamoylmethyl)-1,4-diazo-niabicyclo[2.2.2]oct-1-ylmethyl]-9-oxo-9*H*-fluoren-4-yloxy]-1(*E*)-propenyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylate chloride



C35 H39 Cl N4 O7; Mol wt: 663.1671

ACTION – Carbapenem antibiotic for the treatment of infections caused by Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS).

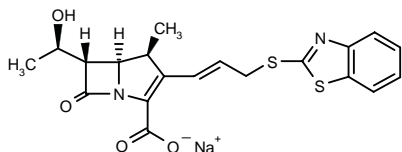
SOURCE – Merck & Co.

REFERENCES

1. Dininno, F.P. and Dykstra, K.D. (Merck & Co., Inc.) *Fused phenoxymethyl carbapenem antibacterials*. WO 9962907.

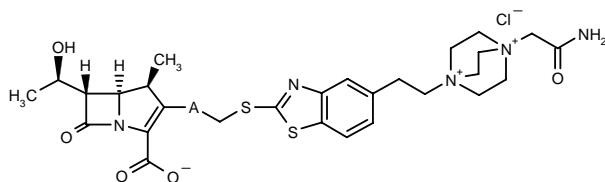
284260

(1*S*,5*R*,6*S*)-2-[3-(Benzothiazol-2-ylsulfanyl)-1(*E*)-propenyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid sodium salt

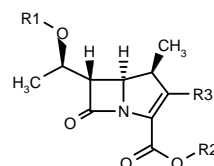


C20 H19 N2 Na O4 S2; Mol wt: 438.5021

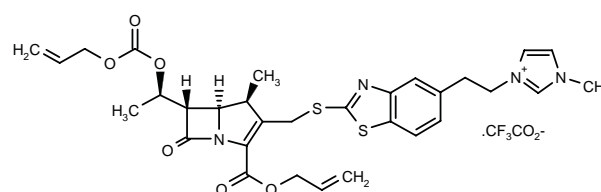
ACTION – Carbapenem antibiotic for the treatment of infections caused by Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other specifically claimed compounds from this series of benzothiazolylthiomethyl carbapenem derivatives include the following:



Compound	A	Formula
284261	(<i>E</i>)-CH=CH-	C ₃₀ H ₃₈ N ₅ O ₅ S ₂ .Cl
284262	ethynylene	C ₃₀ H ₃₆ N ₅ O ₅ S ₂ .Cl



Compound	R1	R2	R3	Formula
284263	allyl-OCO	allyl	2-benzothiazolyl-SCH2	C ₂₅ H ₂₆ N ₂ O ₆ S ₂
284264	H	Na	5-(1-Me-1 <i>H</i> -imidazol-3-ium-3-yl)-CH2CH2)-2-benzothiazolyl-SCH2	C ₂₄ H ₂₆ N ₄ O ₄ S ₂
284265	H	Na	benzothiazol-2-yl-SCH2	C ₁₈ H ₁₇ N ₂ NaO ₄ S ₂
284267	allyl-OCO	allyl	5-(OHCH2CH2)-2-benzothiazolyl-SCH2	C ₂₇ H ₃₀ N ₂ O ₇ S ₂



284268: C31 H35 N4 O6 S2 . C2 F3 O2

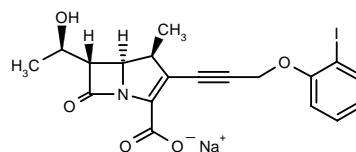
SOURCE – Merck & Co.

REFERENCES

1. Dininno, F.P. et al. (Merck & Co., Inc.) *Benzothiazolylthiomethyl carbapenem antibacterial*. WO 9962906.

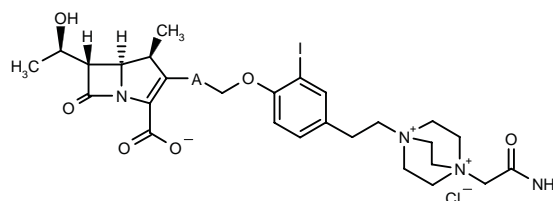
284269

(1*S*,5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-[3-(2-iodophenoxy)-1-propynyl]-1-methyl-1-carba-2-penem-3-carboxylic acid sodium salt



C19 H17 I N Na O5; Mol wt: 489.2353

ACTION – Carbapenem antibiotic agent active against Gram-positive microorganisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other specifically claimed compounds within this series of carbapenems substituted with a cationic group include the following:



Compound	A	Formula
284270	-ethynylene-	C ₂₉ H ₃₆ ClIN ₄ O ₆
284271	(<i>E</i>)-CH=CH-	C ₂₉ H ₃₈ ClIN ₄ O ₆

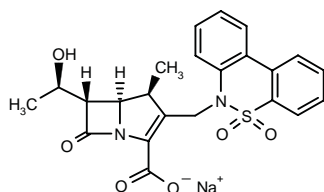
SOURCE – Merck & Co.

REFERENCES

1. Dininno, F.P. and Dykstra, K.D. (Merck & Co., Inc.) *Carbapenem antibacterial cpds., compsns. containing such cpds. and methods of treatment.* WO 9962878.

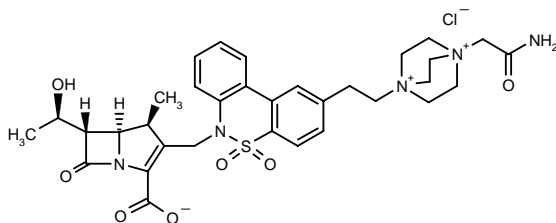
284742

(1*S*,5*R*,6*S*)-2-(5,5-Dioxo-6*H*-dibenzo[*c,e*][1,2]thiazin-6-ylmethyl)-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid sodium salt



C23 H21 N2 Na O6 S; Mol wt: 476.4829

ACTION – Carbapenem antibiotic useful against Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Another exemplified compound from this series of carbapenem derivatives substituted at the 2-position with a 9,9-dioxo-10*H*-9-thia-10-azaphenanthrene-methyl group is:



284743: C33 H40 Cl N5 O7 S

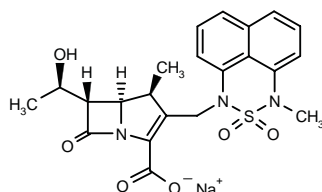
SOURCE – Merck & Co.

REFERENCES

1. Ratcliffe, R.W. et al. (Merck & Co., Inc.) *Carbapenem antibacterial cpds., compsns. containing such cpds. and methods of treatment.* WO 9966928.

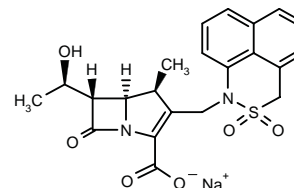
284744

(1*S*,5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-(3-methyl-2,2-dioxo-1*H*,3*H*-naphtho[1,8-*cd*][1,2,6]thiadiazin-1-ylmethyl)-1-carba-2-penem-3-carboxylic acid sodium salt

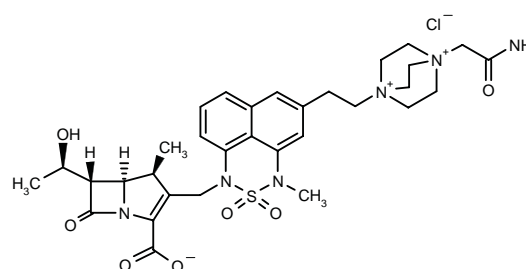


C22 H22 N3 Na O6 S; Mol wt: 479.4868

ACTION – Carbapenem antibiotic useful against Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other exemplified compounds from this series of carbapenem derivatives substituted at the 2-position include the following:



284746: C22 H21 N2 Na O6 S



284748: C32 H41 Cl N6 O7 S

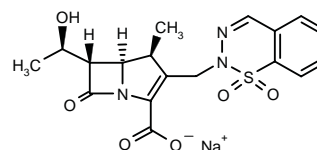
SOURCE – Merck & Co.

REFERENCES

1. Ratcliffe, R.W. and Blizzard, T.A. (Merck & Co., Inc.) *Carbapenem antibacterial cpds., compsns. containing such cpds. and methods of treatment.* WO 9966927.

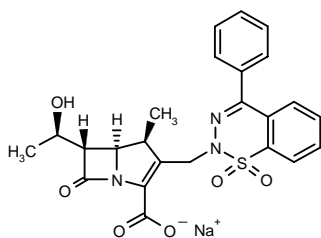
284915

(1*S*,5*R*,6*S*)-2-(1,1-Dioxo-1,2,3-benzothiadiazin-2-ylmethyl)-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid sodium salt

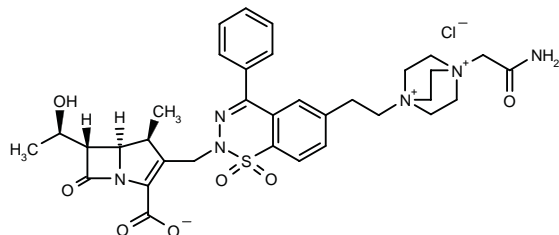


C18 H18 N3 Na O6 S; Mol wt: 427.4112

ACTION – Carbapenem antibiotic useful against Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other exemplified compounds from this series of carbapenem derivatives substituted at the 2-position with a 1,1-dioxo-2*H*-1-thia-2,3-diazanaphthyl-methyl group include the following:



284916: C₂₄ H₂₂ N₃ Na O₆ S



284917: C₃₄ H₄₁ Cl N₆ O₇ S

SOURCE – Merck & Co.

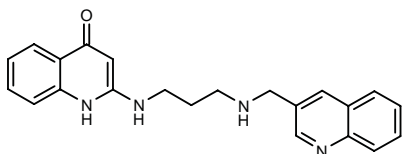
REFERENCES

1. Ratcliffe, R.W. et al. (Merck & Co., Inc.) (*Heterocyclic*)methyl subst. carbapenem antibacterials. WO 9967240.

ANTIBACTERIAL DRUGS

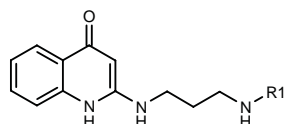
282709

2-[3-(3-Quinolylmethylamino)propylamino]quinolin-4(1*H*)-one

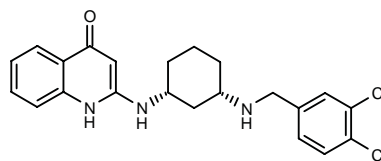


C₂₂ H₂₂ N₄ O; Mol wt: 358.4428

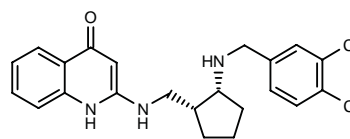
ACTION – Antibacterial agent active against Gram-positive and Gram-negative bacteria, a potent and selective inhibitor of bacterial methionyl t-RNA synthetase (MRS) with no effect on mammalian (rat) enzyme at concentrations up to 10 μM. Other specifically claimed compounds within this series of quinolone derivatives include the following:



Compound	R1	Formula
282710	3,4-(Cl)2-PhCH ₂	C ₁₉ H ₂₀ Cl ₂ N ₃ O
282713	3,4,5-(Br)3-PhCH ₂	C ₁₉ H ₁₈ Br ₃ N ₃ O
282714	5,7-(Me)2-1,2,3,4-tetrahydro-1-Naph	C ₂₄ H ₂₉ N ₃ O
282715	4,5-(Br)2-2-furyl-CH ₂	C ₁₇ H ₁₇ Br ₂ N ₃ O ₂
282717	3,4,5-(Br)3-2-thienyl-CH ₂	C ₁₇ H ₁₆ Br ₃ N ₃ OS



282712: C₂₂ H₂₃ Cl₂ N₃ O



282718: C₂₂ H₂₃ Cl₂ N₃ O

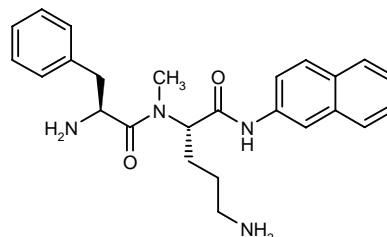
SOURCE – SmithKline Beecham.

REFERENCES

1. Berge, J.M. et al. (SmithKline Beecham plc) *Quinolones used as MRS inhibitors and bactericides*. WO 9955677.

283442

L-Phenylalanyl-*N*²-methyl-L-ornithine (2-naphthyl)amide



C₂₅ H₃₀ N₄ O₂; Mol wt: 418.5380

ACTION – *Pseudomonas aeruginosa* efflux pump inhibitor with minimal intrinsic antibacterial activity (MIC = 256 μg/ml) but able to strongly potentiate (8-fold at 5 μg/ml) the antibacterial activity of levofloxacin against *P. aeruginosa* PAM1032 overexpressing multidrug-resistant efflux pumps. *In vivo*, combination with compound (30 mg/kg i.p.) was able to potentiate the activity of levofloxacin (30 mg/kg s.c.) in *P. aeruginosa* PAM1032-infected mice. Structural modifications are currently being evaluated in an attempt to optimize its pharmacological profile.

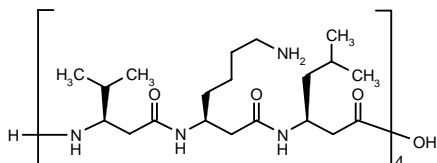
SOURCES – Daiichi Pharmaceutical; Microcide.

REFERENCES

1. Chamberland, S. et al. (Microcide Pharmaceuticals, Inc.) *Efflux pump inhibitors*. WO 9937667.
2. Renau, T.E. et al. *Inhibitors of efflux pumps in Pseudomonas aeruginosa potentiate the activity of fluoroquinolone antibacterial levofloxacin*. J Med Chem 1999, 42(24): 4928.
3. Renau, T.E. et al. *Inhibitors of efflux pumps in Pseudomonas aeruginosa potentiate the activity of the fluoroquinolone antibacterial levofloxacin*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F1265.

284280

β^3 -L-Valyl- β^3 -L-lysyl- β^3 -L-leucyl- β^3 -L-valyl- β^3 -L-lysyl- β^3 -L-leucyl- β^3 -L-valyl- β^3 -L-lysyl- β^3 -L-leucyl- β^3 -L-valyl- β^3 -L-lysyl- β^3 -L-leucine



C80 H154 N16 O13; Mol wt: 1548.1960

ACTION – Antibacterial lead from a class of basic, amphiphilic β -peptides that mimic the activities of natural membrane-active antibiotics and are resistant to enzymatic degradation; these peptides form α -helices, which kill cells by disrupting the structural integrity of the phospholipid membranes. The peptide was able to suppress the growth of *Escherichia coli* with an IC_{50} of 2.1 μ M but exhibited low selectivity for bacterial versus mammalian cells, with a hemolytic concentration required to lyse 50% of human erythrocytes (HD_{50}) of 4.2 μ M.

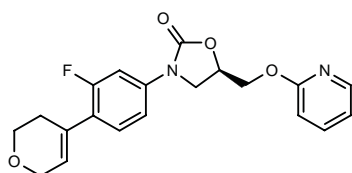
SOURCE – University of Pennsylvania, Philadelphia, PA (US).

REFERENCES

1. Hamuro, Y. et al. *De novo design of antibacterial β -peptides*. J Am Chem Soc 1999, 121(51): 12200.

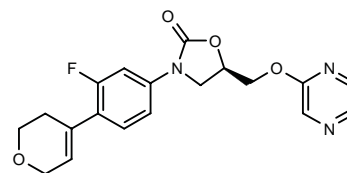
284291

3-[4-(3,6-Dihydro-2H-pyran-4-yl)-3-fluorophenyl]-5(*R*)-(2-pyridyloxymethyl)oxazolidin-2-one



C20 H19 F N2 O4; Mol wt: 370.3781

ACTION – Oxazolidinone antibacterial agent with useful activity against Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCNS), and in particular against strains exhibiting resistance to vancomycin and against *Enterococcus faecium* strains resistant to both aminoglycosides and clinically used β -lactams. *In vitro*, compound was active against *S. aureus* Oxford (MIC = 0.5 μ g/ml), novobiocin-resistant *S. aureus* (MIC = 2.0 μ g/ml), methicillin/quinolone-resistant *S. aureus* (MIC = 1.0 μ g/ml), methicillin-sensitive and methicillin-resistant coagulase-negative staphylococci (MIC = 0.5 and 1.0 μ g/ml, respectively), *Streptococcus pyogenes* C203 (MIC = 2.0 μ g/ml), *Enterococcus faecalis* (MIC = 2.0 μ g/ml) and *Bacillus subtilis* (MIC = 0.5 μ g/ml). Another specifically claimed compound is:



284292: C19 H18 F N3 O4

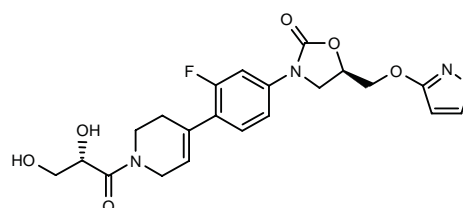
SOURCE – AstraZeneca.

REFERENCES

1. Gravestock, M.B. (Zeneca Ltd.) *Oxazolidinone derivs., process for their preparation and pharmaceutical compns. containing them*. WO 9964416.

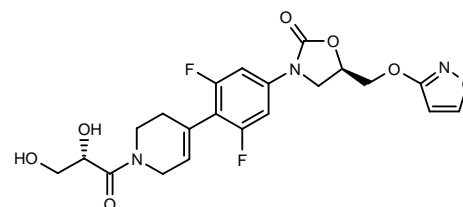
284302

3-[4-[1-[2(*S*),3-Dihydroxypropionyl]-1,2,3,6-tetrahydropyridin-4-yl]-3-fluorophenyl]-5(*R*)-(isoxazol-3-yloxy-methyl)oxazolidin-2-one



C21 H22 F N3 O7; Mol wt: 447.4168

ACTION – Oxazolidinone antibacterial agent reported to possess useful activity against Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCNS), and particularly against strains exhibiting resistance to vancomycin and against *Enterococcus faecium* strains resistant to aminoglycosides and β -lactams. *In vitro*, compound exhibited MIC values of 0.25, 0.5, 0.5, 0.13, 0.5, 0.5, 1.00 and 0.25 μ g/ml against Oxford, novobiocin-resistant and methicillin/quinolone-resistant strains of *S. aureus*, MRCNS, *Streptococcus pyogenes* C203, *Enterococcus faecalis* and *Bacillus subtilis*, respectively. Another specifically claimed compound is:



284303: C21 H21 F2 N3 O7

SOURCE – AstraZeneca.

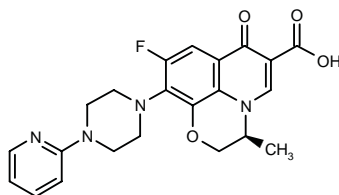
REFERENCES

1. Gravestock, M.B. (Zeneca Ltd.) *Oxazolidinone derivs., process for their preparation and pharmaceutical compns. containing them*. WO 9964417.

YH-6

283577

(-)-9-Fluoro-3(*S*)-methyl-7-oxo-10-[4-(2-pyridinyl)-piperazin-1-yl]-3,7-dihydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid



C22 H21 F N4 O4; Mol wt: 424.4299

ACTION – Quinolone antibacterial agent with activity against *Mycoplasma hominis*, *Mycoplasma orale*, *Mycoplasma salivarium* and *Ureaplasma urealyticum* (MIC = 500, 125, 125 and 250 µg/l, respectively). Compound has comparable activity to the macrolides erythromycin and leucomycin and was at least 2-fold more potent than other quinolones, for which MIC values ranged from 500 to 8000 µg/l. It was also found effective against tetracycline- and erythromycin-resistant *M. hominis* (MIC = 500 µg/l) and *U. urealyticum* strains (MIC = 500 and 250 µg/l, respectively).

SOURCE – Chinese Academy of Sciences, Beijing (CN).

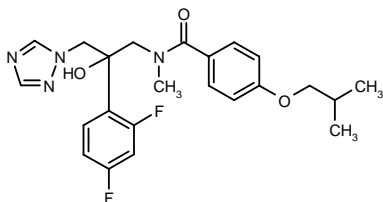
REFERENCES

1. Ye, H. et al. Antimycoplasmal activity of (S)-(-)-9-fluoro-2,3-dihydro-3-methyl-10-[4-(2-pyridinyl)-1-piperazinyl]-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid (YH-6) in comparison with other antibiotics in vitro. Acta Pharmacol Sin 1999, 20(11): 1031.

ANTIFUNGAL AGENTS

283766

N-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-isobutoxy-*N*-methylbenzamide



C23 H26 F2 N4 O3; Mol wt: 444.4794

ACTION – Antifungal agent, an inhibitor of fungal cytochrome P-450 14α-demethylase especially active against *Candida albicans* and *Candida parapsilosis*.

SOURCE – Second Military Medical University, Shanghai (CN).

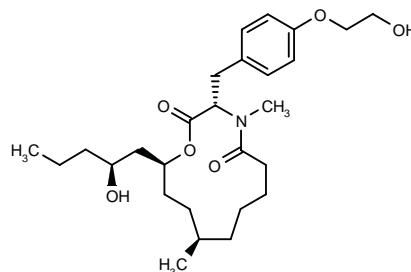
REFERENCES

1. Zhong, W. et al. Synthesis and antifungal activities of 2-(2,4-difluorophenyl)-3-(*N*-methyl-*N*-substituted acylamino)-1-(1*H*-1,2,4-triazol-1-yl)-2-propanol. Acta Pharm Sin 1999, 24(10): 744.

(-)-PF-1163A

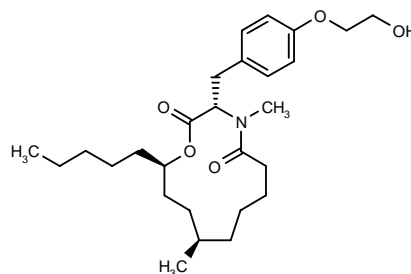
284097

3(*S*)-[4-(2-Hydroxyethoxy)benzyl]-13(*S*)-[2(*S*)-hydroxypentyl]-4,10(*R*)-dimethyl-1-oxa-4-azacyclotridecane-2,5-dione



C27 H43 N O6; Mol wt: 477.6377

ACTION – Antifungal agent extracted from the fermentation broth of *Penicillium* sp., active against *Candida albicans* (MIC = 8 µg/ml); it acts via inhibition of ergosterol biosynthesis (IC₅₀ = 12 ng/ml). Compound did not show cytotoxic activity against human hepatoblastoma HepG2 cells at up to 33.3 µg/ml. Another related compound from this source is:



(-)-PF-1163 B [284098]: C27 H43 N O5

SOURCE – Meiji Seika.

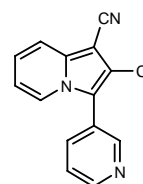
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1. Nose, H. et al. PF1163A and B, new antifungal antibiotics produced by *Penicillium* sp. I. Taxonomy of producing strain, fermentation, isolation and biological activities. J Antibiot 2000, 53(1): 33.
2. Sasaki, T. et al. PF1163A and B, new antifungal antibiotics produced by *Penicillium* sp. II. Physico-chemical properties and structure elucidation. J Antibiot 2000, 53(1): 2000.
3. Tatsuta, K. et al. The total synthesis and absolute structure of antifungal antibiotics (-) PF1163A and B. J Antibiot 1999, 52(12): 1146.

ANTIVIRAL DRUGS

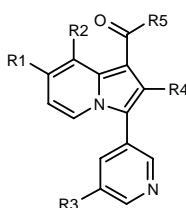
284293

2-Chloro-3-(3-pyridyl)indolizine-1-carbonitrile



C14 H8 Cl N3; Mol wt: 253.6912

ACTION – Antiviral agent for the treatment of infections caused by viruses of the herpesvirus family such as herpes simplex types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), human herpesvirus 6, 7 and 8 (HHV-6, HHV-7 and HHV-8) and Epstein-Barr virus (EBV). In addition, the compound exhibits anti-TNF- α activity, as demonstrated by inhibition of HIV reactivation induced by TNF- α or PMA in U1 cells, and thus may be used for the treatment of TNF-mediated diseases such as inflammation, asthma, diabetes, cachexia, gastrointestinal disorders such as Crohn's disease, CNS disorders, immune disorders, ischemia/reperfusion injury, HIV infection and tuberculosis. Within this series of pyrrole derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	R4	R5	Formula
284294	H	H	H	Cl	NH ₂	C ₁₄ H ₁₀ ClN ₃ O
284295	H	H	H	H	NH ₂	C ₁₄ H ₁₁ N ₃ O
284296	Cl	H	H	Cl	NH ₂	C ₁₄ H ₉ Cl ₂ N ₃ O
284297	H	H	H	Me	OMe	C ₁₆ H ₁₄ N ₂ O ₂
284298	H	OH	H	Cl	NH ₂	C ₁₄ H ₁₀ ClN ₃ O ₂
284299	H	H	Br	Cl	NH ₂	C ₁₄ H ₉ BrClN ₃ O
284300	H	H	H	Me	NH ₂	C ₁₅ H ₁₃ N ₃ O
284301	H	H	H	CN	NH ₂	C ₁₅ H ₁₀ N ₄ O

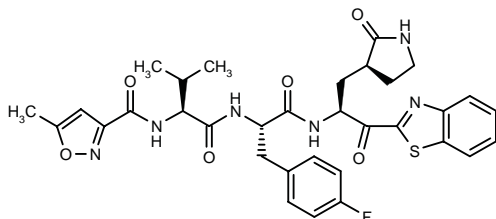
SOURCE – Aventis Pharma.

REFERENCES

1. Mignani, S. and Nemecek, C. (Rhône-Poulenc Rorer SA) *Pyrrole derivs., preparation method and pharmaceutical compsns. containing same*. FR 2779724, WO 9964419.

284573

N-[1(*S*)-[*N*-[1(*S*)-[*N*-1(*S*)-(1,3-Benzothiazol-2-yl)carbonyl-2-[2-oxopyrrolidin-3(*S*)-yl]ethyl]carbamoyl]-2-(4-fluorophenyl)ethyl]carbamoyl]-2-methylpropyl]-5-methylisoxazole-3-carboxamide



C33 H35 F N6 O6 S; Mol wt: 662.7395

ACTION – Antiviral agent, a potent and reversible inhibitor of human rhinovirus (HRV) 3C protease ($K_i = 4.5$ nM) with submicromolar antiviral activity against several rhinovirus serotypes including HRV-14, HRV-1A and HRV-10 ($EC_{50} = 0.34$, 0.34 and 0.25 μ M, respectively). Compound did not exhibit significant cytotoxicity when tested in cell culture ($CC_{50} > 250$ μ M).

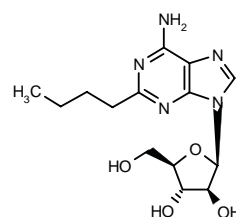
SOURCE – Agouron (Warner-Lambert).

REFERENCES

1. Dragovich, P.S. et al. *Structure-based design of ketone-containing, tripeptidyl human rhinovirus 3C protease inhibitors*. Bioorg Med Chem Lett 2000, 10(1): 45.

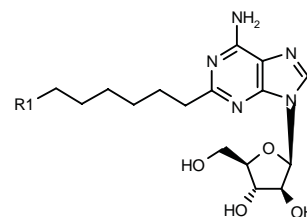
284767

9-(β -D-Arabinofuranosyl)-2-butyladenine



C₁₄ H₂₁ N₅ O₄; Mol wt: 323.3509

ACTION – Antiviral agent for the treatment of diseases caused by DNA viruses such as herpes simplex virus (HSV), varicella-zoster virus, cytomegalovirus (CMV), adenovirus, hepatitis virus and vaccinia virus, a derivative of vidarabine with comparable antiviral activity. Contrary to the parent compound, it is resistant to metabolism by adenosine deaminase (ADA), which makes it suitable for oral administration. Other compounds from this series of arabinosyladenine derivatives include the following:



Compound	R1	Formula
284768	H	C ₁₆ H ₂₅ N ₅ O ₄
284769	Et	C ₁₈ H ₂₉ N ₅ O ₄
284770	C ₆ H ₁₃	C ₂₂ H ₃₇ N ₅ O ₄

SOURCE – Nippon Zoki.

REFERENCES

1. Yamada, T. and Yamanishi, K. (Nippon Zoki Pharmaceutical Co., Ltd.) *Novel arabinosyladenine derivs*. EP 0967220, JP 2000007695.

MSI-591^{*},1-3,5**207344****Octanoyl-leucyl-lysyl-lysyl-leucyl-leucyl-lysyl-lysyl-leucyl-lysyl-leucinamide**

C74 H144 N18 O12; Mol wt: 1478.0660

ACTION – Antiviral agent active against herpes simplex virus type 1 (HSV-1), proven to reduce HSV-1 plaque-forming units in Vero cells in a concentration-dependent manner (55, 76 and 96% inhibition, respectively, at 12.5, 25 and 50 μ M). Pretreatment of HSV with compound prior to inoculation into Vero cells enhanced its antiviral effect, suggesting that it may exert its action by a direct interaction with HSV. Other magainin peptide derivatives include the following:

Glycyl-isoleucyl-glycyl-lysyl-phenylalanyl-leucyl-histidyl-seryl-alanyl-lysyl-lysyl-phenylalanyl-glycyl-lysyl-alanyl-phenylalanyl-valyl-glycyl-glutamyl-isoleucyl-methionyl-asparaginy-serinamide**MSI-500** [220682]⁵⁻⁸: C114 H181 N31 O28 S**Alanyl-leucyl-seryl-lysyl-alanyl-leucyl-seryl-lysyl-alanyl-leucyl-seryl-lysyl-alanyl-leucyl-seryl-lysyl-alanyl-leucyl-seryl-lysine****MSI-12** [282047]^{4,5}: C108 H201 N31 O30**Arginyl-glycyl-glycyl-lysyl-isoleucyl-alanyl-glycyl-lysyl-isoleucyl-alanyl-lysyl-isoleucyl-alanyl-glycyl-lysyl-isoleucyl-alanyl-lysyl-isoleucyl-alanyl-glycyl-lysyl-isoleucyl-alaninamide****MSI-248** [282048]⁵: C106 H198 N34 O24**Glycyl-methionyl-alanyl-seryl-lysyl-alanyl-glycyl-alanyl-isoleucyl-alanyl-glycyl-lysyl-isoleucyl-alanyl-lysyl-valyl-alanyl-leucyl-lysyl-alanyl-leucinamide****MSI-499** [282049]⁵: C88 H162 N26 O22 S**Octanoyl-homoarginyl-isoleucyl-alanyl-glycyl-homoarginyl-isoleucyl-alanyl-homoarginyl-isoleucyl-alanyl-glycyl-homoarginyl-isoleucyl-alanyl-homoarginyl-isoleucyl-alanyl-glycyl-homoarginyl-isoleucyl-alanine****MSI-1251** [282050]⁵: C110 H205 N39 O23**SOURCE** – Magainin.**REFERENCES**

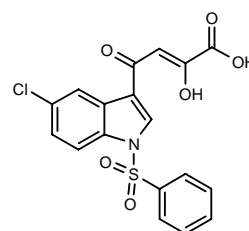
- Hendi, M. et al. (Magainin Pharmaceuticals Inc.) *Treatment of septic shock with conjugated biologically active peptides*. EP 0672053, JP 1996504210, WO 9413697.
- Kari, U. (Magainin Pharmaceuticals Inc.) *Biologically active peptides having N-terminal substitutions*. EP 0644769, US 5654274, US 5686563, WO 9324138, WO 9519370.
- Kari, U.P. et al. (Magainin Pharmaceuticals Inc.) *Biologically active peptides with reduced toxicity in animals and a method for preparing same*. WO 9903488.
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^{*}Identified compound **207344** (see **205546**) Drug Data Rep 1994, 016(05): 0486.

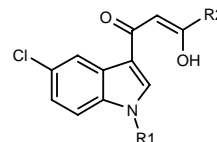
AIDS MEDICINES**282875**

4-[5-Chloro-1-(phenylsulfonyl)-1*H*-indol-3-yl]-2-hydroxy-4-oxo-2-butenic acid



C18 H12 Cl N O6 S; Mol wt: 405.8128

ACTION – Antiviral agent for AIDS, an inhibitor of HIV integrase (IC₅₀ = 0.13 μ g/ml). Other compounds from this series of indole derivatives include the following:



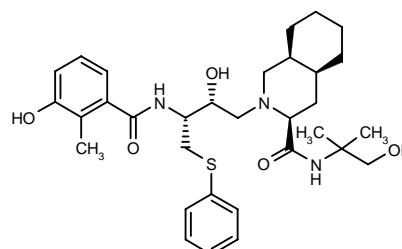
Compound	R1	R2	Formula
282876	H	CO ₂ H	C ₁₂ H ₉ ClNO ₄
282877	H	2H-tetrazol-5-yl	C ₁₂ H ₈ ClN ₅ O ₂
282879	H	1,2,4-triazol-3-yl	C ₁₃ H ₈ ClN ₄ O ₂
282880	2-thienyl-SO ₂	2H-tetrazol-5-yl	C ₁₆ H ₁₀ ClN ₅ O ₄ S ₂
282881	CH ₂ Ph	2H-tetrazol-5-yl	C ₁₉ H ₁₄ ClN ₅ O ₂

SOURCE – Shionogi.**REFERENCES**

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284141

(3*S*,4*aS*,8*aS*)-*N*-(2-Hydroxy-1,1-dimethylethyl)-2-[2(*R*)-hydroxy-3(*R*)-(3-hydroxy-2-methylbenzamido)-4-(phenylsulfonyl)butyl]perhydroisoquinoline-3-carboxamide



C32 H45 N3 O5 S; Mol wt: 583.7895

ACTION – Antiviral agent for AIDS, an inhibitor of HIV protease ($K_i = 5.6 \pm 0.91$ nM). Antiviral activity was demonstrated in HIV-1 RF-infected CEM cells ($IC_{95} = 154.1$ nM) and in HIV-1 IIIB-infected MT-2 cells ($IC_{95} = 92.6$ nM), showing low cytotoxicity in both cases ($TC_{50} = 96.6$ and 92.6 μ M, respectively).

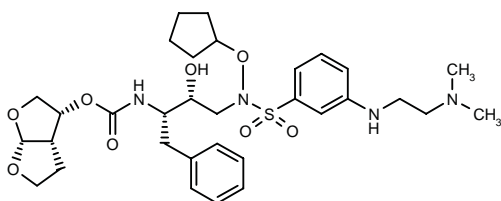
SOURCE – Agouron (Warner-Lambert).

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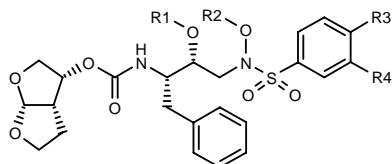
284627

N-[1(*S*)-Benzyl-3-[*N*-(cyclopentyloxy)-3-[2-(dimethylamino)ethylamino]phenylsulfonamido]-2(*R*)-hydroxypropyl]carbamic acid (3*R*,3*aS*,6*aR*)-perhydrofuro[2,3-*b*]furan-3-yl ester



C32 H46 N4 O8 S; Mol wt: 646.8014

ACTION – Antiviral agent for AIDS that acts by inhibiting HIV-1 protease ($K_i < 1$ nM); antiviral activity was demonstrated in infected MT-4 cells ($IC_{50} = 0.1$ μ M or less). Other specifically claimed compounds from this series of sulfonamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
284630	H	cyclopentyl	H	NHMe	$C_{29}H_{39}N_3O_8S$
284632	H	cyclopentyl	H	NH2	$C_{28}H_{37}N_3O_8S$
284633	H	cyclopentyl	OMe	H	$C_{29}H_{38}N_3O_9S$
284634	PO3H2	cyclopentyl	H	NH2	$C_{28}H_{36}N_3O_{11}PS$
284635	H	CH(Et)2	-OCH2O-		$C_{29}H_{38}N_2O_{10}S$
284637	H	4-THP	-OCH2O-		$C_{29}H_{36}N_2O_{11}S$

SOURCE – Vertex.

REFERENCES

1. Sherrill, R.G. et al. (Vertex Pharmaceuticals Inc.) *Sulfonamide inhibitors of aspartyl protease*. WO 9965870.

CYCLOVIOLIN A

284365

L-Seryl-L-cysteinyll-L-valyl-L-phenylalanyl-L-isoleucyl-L-prolyl-L-cysteinyll-L-isoleucyl-L-seryl-L-alanyl-L-alanyl-L-isoleucylglycyl-L-cysteinyll-L-seryl-L-cysteinyll-L-lysyl-L-asparaginyll-L-lysyl-L-valyl-L-cysteinyll-L-tyrosyl-L-arginyl-L-asparaginyllglycyl-L-valyl-L-isoleucyl-L-prolyl-L-cysteinyllglycyl-L-glutamic acid *N*-2.1-*C*-1.31-lactam *S*-3.2-*S*-3.16:*S*-3.7-*S*-3.21:*S*-3.14-*S*-3.29-tris(disulfide)

C137 H216 N38 O39 S6; Mol wt: 3211.8360

ACTION – Anti-HIV agent, a macrocyclic peptide isolated from the tropical plant *Leonia cymosa*, a genus of the Violaceae plant family. Compound exhibited an antiviral EC_{50} value of about 130 nM against HIV-1-infected CEM-SS cells, with relatively low cytotoxicity to host cells ($IC_{50} \sim 560$ nM). Other related compounds extracted from the plant are:

L-Seryl-L-cysteinyll-L-tyrosyl-L-valyl-L-leucyl-L-prolyl-L-cysteinyll-L-phenylalanyl-L-threonyll-L-valylglycyl-L-cysteinyll-L-threonyll-L-cysteinyll-L-threonyll-L-seryl-L-seryl-L-glutaminyll-L-cysteinyll-L-phenylalanyl-L-lysyl-L-asparaginyllglycyl-L-threonyll-L-alanyl-L-cysteinyllglycyl-L-glutamic acid *N*-2.1-*C*-1.29-lactam *S*-3.2-*S*-3.14:*S*-3.7-*S*-3.19:*S*-3.12-*S*-3.26-tris(disulfide)

Cycloviolins B [284366]: C120 H177 N31 O40 S6

L-Seryl-L-cysteinyll-L-valyl-L-phenylalanyl-L-isoleucyl-L-prolyl-L-cysteinyll-L-leucyl-L-threonyll-L-threonyll-L-valyl-L-alanylglycyl-L-cysteinyll-L-seryl-L-cysteinyll-L-lysyl-L-asparaginyll-L-lysyl-L-valyl-L-cysteinyll-L-tyrosyl-L-arginyl-L-asparaginyllglycyl-L-isoleucyl-L-prolyl-L-cysteinyllglycyl-L-glutamic acid *N*-2.1-*C*-1.30-lactam *S*-3.2-*S*-3.16:*S*-3.7-*S*-3.21:*S*-3.14-*S*-3.28-tris(disulfide)

Cycloviolins C [284367]: C133 H209 N37 O 39 S6

L-Seryl-L-cysteinyll-L-valyl-L-phenylalanyl-L-isoleucyl-L-prolyl-L-cysteinyll-L-isoleucyl-L-seryl-L-alanyl-L-alanyl-L-isoleucylglycyl-L-cysteinyll-L-seryl-L-cysteinyll-L-lysyl-L-asparaginyll-L-lysyl-L-valyl-L-cysteinyll-L-tyrosyl-L-arginyl-L-asparaginyllglycyl-L-phenylalanyl-L-prolyl-L-cysteinyllglycyl-L-glutamic acid *N*-2.1-*C*-1.30-lactam *S*-3.2-*S*-3.16:*S*-3.7-*S*-3.21:*S*-3.14-*S*-3.28-tris(disulfide)

Cycloviolins D [284368]: C135 H205 N37 O38 S6

SOURCE – National Cancer Institute, Bethesda, MD (US).

REFERENCES

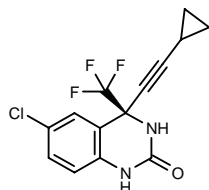
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DPC-961¹⁻⁸

270600

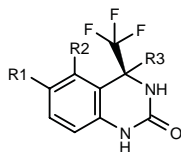
6-Chloro-4-(*S*)-(2-cyclopropylethynyl)-4-(trifluoromethyl)-3,4-dihydro-1*H*-quinazolin-2-one

DMP-961



C₁₄ H₁₀ Cl F₃ N₂ O; Mol wt: 314.6930

ACTION – Anti-HIV agent, a non-nucleoside reverse transcriptase inhibitor (IC₅₀ = 31.8 nM) with antiviral activity against wild-type (IC₉₀ = 2 nM) and mutant variants of HIV-1 including single variants containing the K103N or L101I amino acid substitution (IC₉₀ = 10 and 13 nM, respectively) and double variants containing K103N/V108I, K103N/P225H and K103N/L100I substitutions (IC₉₀ = 38, 73 and 1100 nM, respectively). In comparison to efavirenz, it was 7- and 4-fold more potent against the clinically important K103N/V108I and K103N/P225H double mutants and maintained a high degree of potency against other common mutations induced by NNRTIs such as Y181C and V106A. Due to lower plasma protein binding, the free fraction of compound was increased compared to efavirenz, and plasma levels above 2 µM were reached in monkeys following oral doses of 2 mg/kg, with a half-life of 20-76 h. Pharmacokinetic studies in healthy volunteers demonstrated that when administered once daily at doses of 100, 200, 300 or 400 mg, plasma levels above the IC₉₀ against wild-type, K103N and several clinically important double-mutant HIV-1 viruses were attained. Other related compounds are:



Compound	R1	R2	R3	Formula
DPC-963 [270601] ^{1-4,8-10}	F	F	cyclopropyl-ethynylene	C ₁₄ H ₉ F ₃ N ₂ O
DPC-083 [282908] ^{1,3,5,11}	Cl	H	(<i>E</i>)-cyclopropyl-CH=CH	C ₁₄ H ₁₂ ClF ₃ N ₂ O
DPC-082 [284369] ^{1,3}	F	F	(<i>E</i>)-cyclopropyl-CH=CH	C ₁₄ H ₁₁ F ₃ N ₂ O

SOURCE – DuPont Pharmaceuticals.

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- Corbett, J.W. et al. Discovery of HIV-1 non-nucleoside reverse transcriptase development candidates DMP 961 and DMP 963. AIDS 1998, 12(Suppl. 4): Abst P21.
- Corbett, J.W. et al. Expanded-spectrum nonnucleoside reverse transcriptase inhibitors inhibit clinically relevant mutant variants of human immunodeficiency virus type 1. Antimicrob Agents Chemother 1999, 43(12): 2893.
- Erickson-Viitanen, S. et al. DMP 961 and DMP 963: 2nd generation non-nucleoside reverse transcriptase inhibitors active against the RT K103N mutant. 6th Conf Retroviruses Opportunistic Infect (Jan 31-Feb4, Chicago) 1999, Abst 13.
- Fiske, W.D. et al. Pharmacokinetics of a second-generation NNRTI, DPC 083, after multiple oral doses in healthy volunteers. 7th Conf Retroviruses Opportunistic Infect (Jan 30-Feb 2, San Francisco) 2000, Abst 99.

6. Jeffrey, S. et al. In vitro NNRTI resistance of recombinant HIV carrying mutations observed in efavirenz treatment failures. 6th Conf Retroviruses Opportunistic Infect (Jan 31-Feb 4, Chicago) 1999, Abst 110.

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8. King, R.W. et al. Synergism studies between efavirenz (SUSTIVATM), DMP266 and nucleoside or non-nucleoside inhibitors of the HIV-1 RT. Antivir Res 1999, 41(2): Abst 43.

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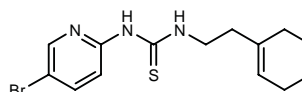
10. Xie, M. and Maurin, M.B. Sublimation characterization of DPC 963 by thermogravimetric analysis and vapor pressure estimation. Annu Meet Am Assoc Pharm Sci (Nov 14-18, New Orleans) 1999, Abst 2342.

11. Xie, M. et al. Sodium lauryl sulfate-catalyzed degradation of DPC 083 in solid state. Annu Meet Am Assoc Pharm Sci (Nov 14-18, New Orleans) 1999, Abst 3478.

HI-346^{1,2,4,5}

281424

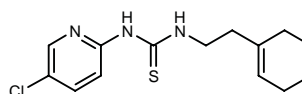
N-(5-Bromopyridin-2-yl)-*N'*-[2-(1-cyclohexenyl)ethyl]-thiourea



C₁₄ H₁₈ Br N₃ S; Mol wt: 340.2872

M.p. 172-3 °C.

ACTION – Anti-HIV agent, an inhibitor of HIV reverse transcriptase (IC₅₀ = 0.4 µM in cell-free medium) that exhibits superior activity against the multidrug-resistant HIV-1 strain RT-MDR than against wild-type HTLV_{IIIB} (IC₅₀ = 0.001 and 0.003 µM, respectively); it was 20-5,000-fold more potent than zidovudine, MKC-442, delavirdine and nevirapine against the MDR HIV-1 strain. When compound was tested against the non-nucleoside inhibitor-resistant HIV-1 strain A17 variant with both Y181C and K103N mutations in RT, it demonstrated superior activity to nevirapine, zidovudine and delavirdine, although its activity was markedly reduced (IC₅₀ = 18.7 µM). No cytotoxicity was seen at effective concentrations. Another cyclohexenyl-containing thiourea compound with a similar profile of activity is:



HI-445 [281425]¹⁻⁵: C₁₄ H₁₈ Cl N₃ S

SOURCES – Hughes Institute, Roseville, MN (US); Medivir.

REFERENCES

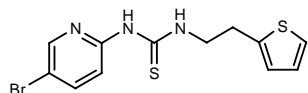
- Lind, P.T. et al. (Medivir AB) Cpd. and methods for inhibition of HIV and related viruses. EP 0706514, JP 1997502702, WO 9506034.
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- Uckun, F.M. et al. Inhibitors of multidrug-resistant human immunodeficiency virus-1: Thiourea derivatives HI-346 and HI-445. 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 3373.

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HI-443

284362

N-(5-Bromopyridin-2-yl)-*N'*-[2-(2-thienyl)ethyl]thiourea



C12 H12 Br N3 S2; Mol wt: 342.2838

M.p. 160-1 °C.

ACTION – Anti-HIV agent, an inhibitor of reverse transcriptase (IC_{50} = 0.8 μ M) with similar potency to nevirapine against HIV-1 strain HTLV_{IIIB} in human peripheral blood mononuclear cells (IC_{50} = 0.03 and 0.034 μ M, respectively); however, compound was 50- to over 1,000-fold more potent than nevirapine, delavirdine, MKC-442 and zidovudine (AZT), and 5 times more potent than zalcitabine, against the multidrug-resistant strain RT-MDR bearing a V106A mutation (IC_{50} = 0.004 μ M) as well as 10- to over 2,000-fold more potent than zalcitabine, nevirapine and delavirdine against non-nucleoside reverse transcriptase inhibitor-resistant strains (IC_{50} = 0.048 μ M against HIV-1 A17 with Y181C mutation). It was also active against the zalcitabine-resistant HIV-1 A17 variant with a double mutation (Y181C and K103N), giving an IC_{50} of 3.3 μ M. Animal studies demonstrated its safety at doses 100 times higher than those providing effective antiviral concentrations.

SOURCE – Hughes Institute, Roseville, MN (US).

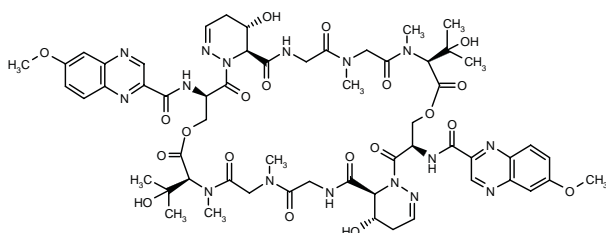
REFERENCES

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QUINOXAPEPTIN C

283645

Bis[*N*-(6-methoxyquinoxalin-2-ylcarbonyl)-D-seryl-2,3,4,5-tetrahydro-4(*S*)-hydroxypyridazin-3(*S*)-ylcarbonyl]glycyl-*N*-methylglycyl-3-hydroxy-*N*-methyl-L-valine]-(5→1'),(5'→1)-dilactone



C58 H72 N16 O20; Mol wt: 1313.2990

$[\alpha]_D^{20}$ -66° (*c* 0.18, *CHCl*₃).

ACTION – Anti-HIV agent, a cyclic depsidecapeptide inhibitor of HIV-1 reverse transcriptase (IC_{50} = 0.3 μ M) devoid of cytotoxicity at up to 100 nM against both mouse leukemia L1210 and human colon carcinoma HCT 116 cells.

SOURCE – Scripps Research Institute, La Jolla, CA (US).

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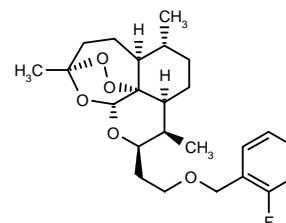
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TREATMENT OF PROTOZOAL DISEASES

284134

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*R*,12*R*,12*aR*)-10-[2-(2-Fluorobenzyloxy)ethyl]-3,6,9-trimethylperhydro-3,12-epoxypyrano[4,3-*j*]-1,2-benzodioxepine

10β-[2-(2-Fluorobenzyloxy)ethyl]-10-deoxoartemisinin



C24 H33 F O5; Mol wt: 420.5177

Clear oil.

ACTION – Antimalarial agent, an artemether derivative with strong *in vitro* activity against chloroquine-sensitive HB3 and chloroquine-resistant K1 strains of *Plasmodium falciparum* (IC_{50} = 0.22 and 1.02 nM, respectively), being 15- and 3-fold more potent than artemisinin, respectively. The antimalarial activity of compound against *Plasmodium berghei*-infected mice was comparable to that of artemether (ED_{50} = 5.08 and 3.15 mg/kg i.p., respectively).

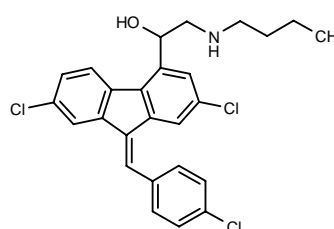
SOURCE – University of Liverpool, Liverpool (GB).

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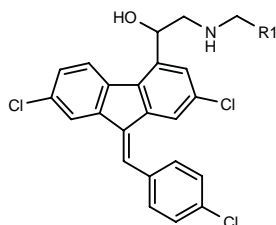
284760

2-(Butylamino)-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9*H*-fluoren-4-yl]ethanol



C26 H24 Cl3 N O; Mol wt: 472.8406

ACTION – Antiparasitic agent for the treatment of diseases caused by protozoa and trematodes, particularly malaria, a derivative of benflumetol with improved activity against plasmodia. When tested against 58 isolates of *Plasmodium falciparum*, compound completely inhibited the great majority of isolates at 100 nmol/l and none of the isolates showed schizont maturation at 300 nmol/l; compound was significantly more effective than benflumetol, as determined by EC_{50} and EC_{99} values of 4.36 and 45.72 nmol/l, respectively, compared to 24.44 and 371.59 nmol/l respectively, for benflumetol. Other compounds from this series of benflumetol derivatives include the following:



Compound	R1	Formula
284761	H	C ₂₃ H ₁₈ Cl ₃ NO
284762	Bu	C ₂₇ H ₂₆ Cl ₃ NO

SOURCE – Novartis.

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NIOSOMAL AMAROGENTIN

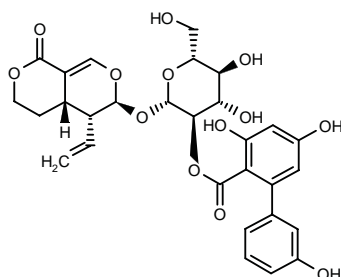
284499

Niosomal formulation containing Span 20 (sorbitan monolaurate):cholesterol:phosphatidic acid in a proportion 1.0:0.5:0.1 and around 24-33% of amarogentin

Amarogentin

284251

(4a*S*,5*R*,6*S*)-5-Ethenyl-6-[2-*O*-(3,3'-5-trihydroxybiphenyl-2-ylcarbonyl)-β-D-glucopyranosyloxy]-4,4a,5,6-tetrahydro-1*H*,3*H*-pyrano[3,4-*c*]pyran-1-one



C29 H30 O13 ; Mol wt: 586.5430

ACTION – Antileishmanial agent, a niosomal formulation of amarogentin, a glycoside extracted from the Indian medicinal plant *Swertia chirata* and able to inhibit DNA topoisomerase I of *Leishmania donovani*. In hamsters infected with *L. donovani*, the niosomal formulation was shown to reduce parasite load in the spleen by 90% after only 6 doses (2.5 mg/kg, corresponding to 2 mg/kg of amarogentin, every 3 days) compared with a 34% reduction with free amarogentin. Toxicity studies involving blood pathology, histological staining of tissues and specific enzyme levels related to normal liver function showed no hepatic or renal toxicity.

SOURCE – Indian Institute of Chemical Biology, Calcutta (IN).

REFERENCES

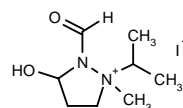
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

281844

2-Formyl-3-hydroxy-1-isopropyl-1-methylpyrazolidin-1-ium iodide



C8 H17 I N2 O2; Mol wt: 300.1343

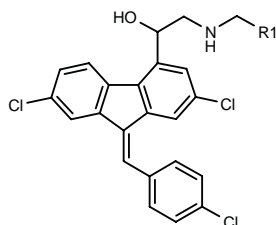
ACTION – Antiinflammatory agent proven to reduce both the exudative and proliferative phases of inflammation in the carrageenan-induced paw edema and cotton pellet-induced granuloma models in rats. It exhibited greater efficacy than diclofenac but lower acute toxicity, inducing no gastric ulcers or suppression of hemopoiesis.

SOURCES – Military Medical Academy, St. Petersburg (RU); St. Petersburg Chemico-Pharmaceutical Academy, St. Petersburg (RU).

REFERENCES

1. Zelenin, K.N. et al. *Anti-inflammatory activity of 2-acetyl-5(3)-hydroxytetrahydro-1*H*-pyrazole derivatives*. Arzneim-Forsch Drug Res 1999, 49(2): 843.

ACTION – Antiparasitic agent for the treatment of diseases caused by protozoa and trematodes, particularly malaria, a derivative of benflumetol with improved activity against plasmodia. When tested against 58 isolates of *Plasmodium falciparum*, compound completely inhibited the great majority of isolates at 100 nmol/l and none of the isolates showed schizont maturation at 300 nmol/l; compound was significantly more effective than benflumetol, as determined by EC₅₀ and EC₉₉ values of 4.36 and 45.72 nmol/l, respectively, compared to 24.44 and 371.59 nmol/l respectively, for benflumetol. Other compounds from this series of benflumetol derivatives include the following:



Compound	R1	Formula
284761	H	C ₂₃ H ₁₈ Cl ₃ NO
284762	Bu	C ₂₇ H ₂₆ Cl ₃ NO

SOURCE – Novartis.

REFERENCES

1. Allmendinger, T. and Wernsdorfer, W.H. (Novartis AG) *Benflumetol derivs., intermediates thereof and their use against parasitological protozoa and trematodes*. WO 9967197.

NIOSOMAL AMAROGENIN

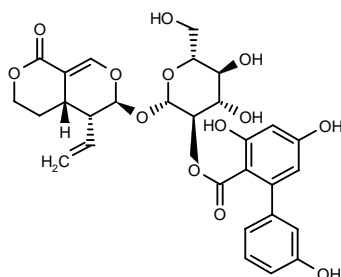
284499

Niosomal formulation containing Span 20 (sorbitan monolaurate):cholesterol:phosphatidic acid in a proportion 1.0:0.5:0.1 and around 24-33% of amarogentin

Amarogentin

284251

(4a*S*,5*R*,6*S*)-5-Ethenyl-6-[2-*O*-(3,3'-5-trihydroxybiphenyl-2-ylcarbonyl)-β-D-glucopyranosyloxy]-4,4a,5,6-tetrahydro-1*H*,3*H*-pyrano[3,4-*c*]pyran-1-one



C29 H30 O13 ; Mol wt: 586.5430

ACTION – Antileishmanial agent, a niosomal formulation of amarogentin, a glycoside extracted from the Indian medicinal plant *Swertia chirata* and able to inhibit DNA topoisomerase I of *Leishmania donovani*. In hamsters infected with *L. donovani*, the niosomal formulation was shown to reduce parasite load in the spleen by 90% after only 6 doses (2.5 mg/kg, corresponding to 2 mg/kg of amarogentin, every 3 days) compared with a 34% reduction with free amarogentin. Toxicity studies involving blood pathology, histological staining of tissues and specific enzyme levels related to normal liver function showed no hepatic or renal toxicity.

SOURCE – Indian Institute of Chemical Biology, Calcutta (IN).

REFERENCES

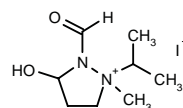
1. Medda, S. et al. *Evaluation of the in-vivo activity and toxicity of amarogentin, an antileishmanial agent, in both liposomal and niosomal forms*. J Antimicrob Chemother 1999, 44(6): 791.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

281844

2-Formyl-3-hydroxy-1-isopropyl-1-methylpyrazolidin-1-ium iodide



C8 H17 I N2 O2; Mol wt: 300.1343

ACTION – Antiinflammatory agent proven to reduce both the exudative and proliferative phases of inflammation in the carrageenan-induced paw edema and cotton pellet-induced granuloma models in rats. It exhibited greater efficacy than diclofenac but lower acute toxicity, inducing no gastric ulcers or suppression of hemopoiesis.

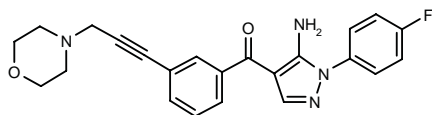
SOURCES – Military Medical Academy, St. Petersburg (RU); St. Petersburg Chemico-Pharmaceutical Academy, St. Petersburg (RU).

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1. Zelenin, K.N. et al. *Anti-inflammatory activity of 2-acetyl-5(3)-hydroxytetrahydro-1*H*-pyrazole derivatives*. Arzneim-Forsch Drug Res 1999, 49(2): 843.

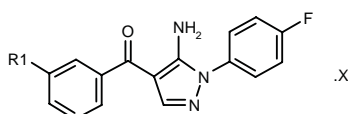
282967

1-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-1-[3-(4-morpholinyl)-1-propynyl]phenylmethanone



C23 H21 F N4 O2; Mol wt: 404.4429

ACTION – Agent for the treatment of inflammatory and autoimmune diseases, an inhibitor of p38 MAP kinase ($IC_{50} = 1.78 \mu M$). Compound was shown to inhibit lipopolysaccharide-induced TNF- α production *in vivo* in rats following oral administration (96% inhibition at 30 mg). Other compounds within this series of pyrazole derivatives include the following:



Compound	R1	X	Formula
282969	4-Me-1-Piz-CH2-ethynylene-	2HCl	C ₂₄ H ₂₄ FN ₅ O ₂ HCl
282971	ethynylene-CH2NHMe		C ₂₀ H ₁₇ FN ₄ O
282973	C(=NOH)NH2		C ₁₇ H ₁₄ FN ₅ O ₂
282974	OCH2CONHMe		C ₁₉ H ₁₇ FN ₄ O ₃

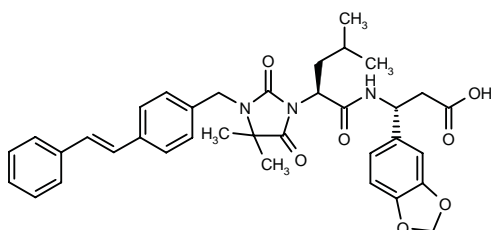
SOURCE – Roche.

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1. Labadie, S.S. et al. (F. Hoffmann-La Roche AG) *Pyrazole derivs. as p-38 MAP kinase inhibitors*. WO 9957101.

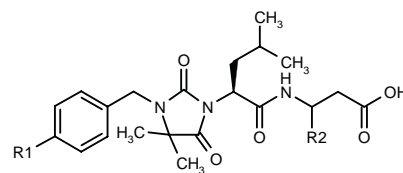
283612

3(R)-(1,3-Benzodioxol-5-yl)-3-[2(S)-[4,4-dimethyl-2,5-dioxo-3-[4-[(E)-2-phenylvinyl]benzyl]imidazolidin-1-yl]-4-methylpentanamido]propionic acid



C36 H39 N3 O7; Mol wt: 625.7181

ACTION – Agent for the treatment or prevention of disorders involving leukocyte adhesion and migration and/or disorders involving adhesion processes mediated by the VLA-4 receptor such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, inflammatory disorders of the CNS, asthma, allergy, cardiovascular disorders, arteriosclerosis, restenosis, diabetes, transplant rejection, cancer and malaria. Compound was found to inhibit the adhesion of U937 cells to hVCAM-1(1-3)-IgG with an IC_{50} value of $0.15 \mu M$. Other compounds from this series of imidazolidine derivatives include the following:



Compound	R1	R2	Isomer	Formula
283613	CH=CHPh	Me	R	C ₃₀ H ₃₇ N ₃ O ₅
283614	CH=CHPh	Ph	R	C ₃₅ H ₃₉ N ₃ O ₅
283615	OCH2Ph	Me	R	C ₂₉ H ₃₇ N ₃ O ₆
283616	2-Me-PhCH=CH	Me	R	C ₃₁ H ₃₉ N ₃ O ₅
283617	2-Me-PhCH=CH	Ph	R	C ₃₆ H ₄₁ N ₃ O ₅

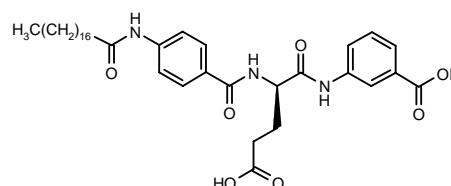
SOURCE – Aventis Pharma.

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1. Neises, B. et al. (Hoechst Marion Roussel Deutschland GmbH) *Imidazolidine derivs., the production thereof, their use and pharmaceutical preparations containing the same*. DE 19821483, WO 9960015.

283955

*N*¹-(3-Carboxyphenyl)-*N*²-[4-(octadecanamido)benzoyl]-D-glutamic acid 1-amide



C37 H53 N3 O7; Mol wt: 651.8397

ACTION – An inhibitor of E-selectin ($IC_{50} = 26 \mu M$), P-selectin ($IC_{50} = 5.5 \mu M$) and L-selectin ($IC_{50} = 4 \mu M$) binding; when tested *in vivo*, it produced 78% inhibition of ovalbumin-induced ear edema and 96% inhibition of myeloperoxidase activity in sensitized mice at 10 mg/kg i.v., as well as 78% inhibition of thioglycolate-induced peritonitis in mice at this dose.

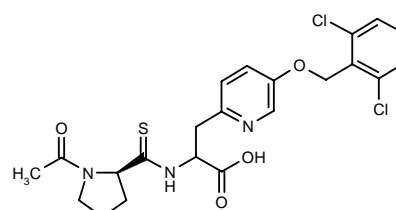
SOURCE – Kanebo (Nippon Organon).

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1. Tsukida, T. et al. (Kanebo, Ltd.) *Amino carboxylate deriv. and agents containing it as effective ingredient*. JP 1999269135.

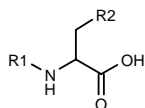
284109

N-Acetyl-D-thiopropyl-3-[5-(2,6-dichlorobenzyloxy)pyridin-2-yl]-DL-alanine



C22 H23 Cl2 N3 O4 S; Mol wt: 496.4127

ACTION – Agent for the treatment of immune or inflammatory disorders that acts by selectively inhibiting the binding of α_4 integrins, particularly $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins, to their ligands. Other specifically claimed compounds from this series of aromatic amine derivatives are:



Compound	R1	R2	Formula
284110	N-Ac-D-thiopropyl	5-(PhSO ₂ O)-2-Pyr	C ₂₁ H ₂₃ N ₃ O ₆ S ₂
284113	2-Cl-3-Pyr-CO	6-[2,6-(Cl)2-PhCONH]-3-Pyr	C ₂₁ H ₁₅ Cl ₃ N ₄ O ₄

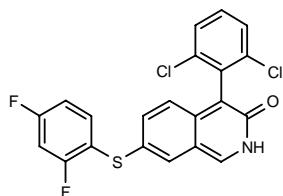
SOURCE – Celltech Chiroscience (Celltech Group).

REFERENCES

1. Head, J.C. et al. (Celltech Chiroscience plc) *Aromatic amine derivs. as pharmaceutical agents*. WO 9962901.

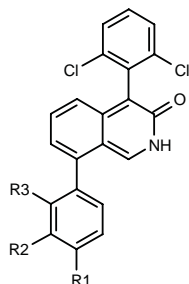
284207

4-(2,6-Dichlorophenyl)-7-(2,4-difluorophenyl)sulfonylisoquinolin-3(2H)-one

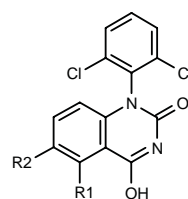


C₂₁ H₁₁ Cl₂ F₂ N O S; Mol wt: 434.2919

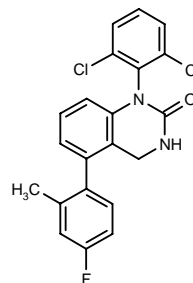
ACTION – Agent for the treatment or prevention of inflammatory, autoimmune or proliferative diseases, destructive bone disorders, infectious diseases, neurodegenerative diseases, allergies, ischemia/reperfusion in stroke, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia or cardiac hypertrophy, an inhibitor of p38 MAP kinase. Other specifically claimed compounds include the following:



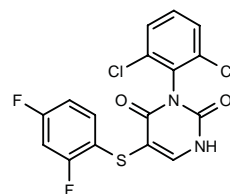
Compound	R1	R2	R3	Formula
284208	F	H	Me	C ₂₂ H ₁₄ Cl ₂ FNO
284209	H	Cl	CH ₂ OH	C ₂₂ H ₁₄ Cl ₃ NO ₂



Compound	R1	R2	Formula
284210	H	2,4-(F)2-PhS	C ₂₀ H ₁₀ Cl ₂ F ₂ N ₂ O ₂ S
284212	2,4-(F)2-Ph	H	C ₂₀ H ₁₀ Cl ₂ F ₂ N ₂ O ₂



284211: C₂₁ H₁₅ Cl₂ F N₂ O



284213: C₁₆ H₈ Cl₂ F₂ N₂ O₂ S

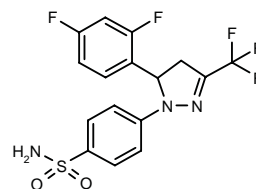
SOURCE – Vertex.

REFERENCES

1. Salituro, F. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of p38*. WO 9964400.

284219

4-[5-(2,4-Difluorophenyl)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl]benzenesulfonamide



C₁₆ H₁₂ F₅ N₃ O₂ S; Mol wt: 405.3458

ACTION – Antiinflammatory agent, a cyclooxygenase type 2 (COX-2) inhibitor with high potency and selectivity for inhibition of PGE₂ production in inflammatory exudate (COX-2) versus gastric mucosa (COX-1) in the carrageenan-induced paw edema model in rats, giving ED₅₀ values of 3.6 and > 40 mg/kg p.o., respectively. Compound was more potent than nimesulide and nabumetone in a rat model of heat-induced hyperalgesia (ED₅₀ = 0.2, 1.0 and 2.1 mg/kg p.o., respectively) and it showed antiarthritic activity in the rat adjuvant-induced arthritis model (71% inhibition of secondary inflammation at 10 mg/kg/day p.o. x 11 days). Moreover, it had no ulcerogenic effect in rats subjected to cold stress (maximal nonulcerogenic dose > 80 mg/kg p.o.), whereas diclofenac and piroxicam were ulcerogenic at much lower doses (maximal nonulcerogenic dose = 1.2 and 1.7 mg/kg p.o., respectively). A representative compound from a series of pyrazoline derivatives.

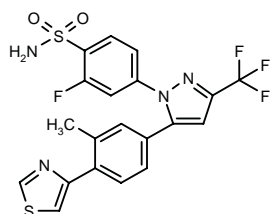
SOURCE – Esteve.

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1. Cuberes-Altisent, M.R. et al. (Laboratorios del Dr. Esteve, SA) *Pyrazoline derivs., their preparation and application as medicaments*. WO 9962884.

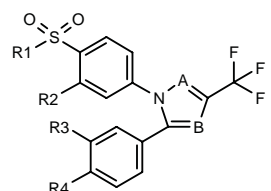
284378

2-Fluoro-4-[5-[3-methyl-4-(thiazol-4-yl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide



C20 H14 F4 N4 O2 S2; Mol wt: 482.4806

ACTION – Cyclooxygenase inhibitor with selectivity for COX-2, useful for alleviating inflammation and related disorders such as arthritis. Other specifically claimed sulfonylbenzene compounds include the following:



Compound	R1	R2	R3	R4	A	B	Formula
284379	Me	H	Cl	4-thiazolyl	N	CH	C ₂₀ H ₁₃ ClF ₃ N ₃ O ₂ S ₂
284380	NH ₂	H	Me	4-oxazolyl	N	CH	C ₂₀ H ₁₅ F ₃ N ₄ O ₃ S
284381	Me	F	H	2-thienyl	N	CH	C ₂₁ H ₁₄ F ₄ N ₂ O ₂ S ₂
284382	Me	F	Cl	2-furyl	N	CH	C ₂₁ H ₁₃ ClF ₄ N ₂ O ₃ S
284384	Me	F	H	4-thiazolyl	CH	N	C ₂₀ H ₁₃ F ₄ N ₃ O ₂ S ₂

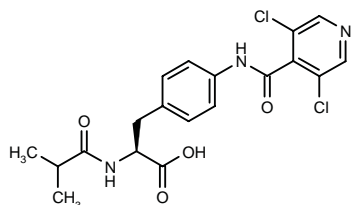
SOURCE – Pfizer.

REFERENCES

1. Ando, K. et al. (Pfizer Inc.) *Sulfonylbenzene cpds. as anti-inflammatory/analgesic agents*. WO 9964415.

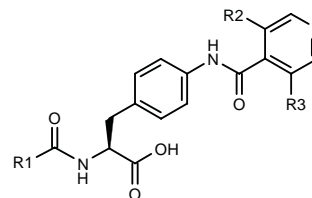
284461

N-(2-Methylpropionyl)-L-4-(3,5-dichloropyridin-4-yl)carboxamido)phenylalanine



C19 H19 Cl2 N3 O4; Mol wt: 424.2821

ACTION – Potent and selective inhibitor of α_4 integrins, particularly $\alpha_4\beta_1$ and/or $\alpha_4\beta_7$, with little or no activity at other α integrins. As such, it is expected to be of use in the treatment or prophylaxis of immune or inflammatory disorders including rheumatoid arthritis, multiple sclerosis, allograft rejection, diabetes, psoriasis, dermatitis, asthma and inflammatory bowel disease. Other specifically claimed phenylalanine derivatives include the following:



Compound	R1	R2	R3	A	Formula
284465	cyclopropyl	Cl	Cl	N	C ₁₉ H ₁₇ Cl ₂ N ₃ O ₄
284466	Me	Cl	Cl	N	C ₁₇ H ₁₅ Cl ₂ N ₃ O ₄
284467	t-Bu	F	F	CH	C ₂₁ H ₂₂ F ₂ N ₂ O ₄
284468	1-adamantyl	Cl	Cl	CH	C ₂₇ H ₂₈ Cl ₂ N ₂ O ₄

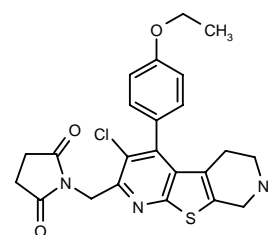
SOURCE – Celltech Chiroscience (Celltech Group).

REFERENCES

1. Porter, J.R. et al. (Celltech Chiroscience plc) *Phenylalanine derivs. as integrin inhibitors*. WO 9964390.

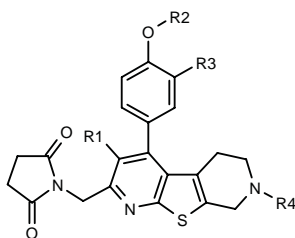
284485

1-[3-Chloro-4-(4-ethoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-b:5,4-c']dipyridin-2-ylmethyl]pyrrolidine-2,5-dione



C23 H22 Cl N3 O3 S; Mol wt: 455.9638

ACTION – Antiinflammatory agent able to suppress hind paw edema in the rat adjuvant arthritis model by 98% at a dose of 3.13 mg/kg/day p.o. for 14 days and highly stable to metabolism by dog liver microsomes. It also exhibited bone resorption-inhibitory activity and the ability to inhibit the production of immunocytokines, e.g., IL-2 and interferon gamma, and is thus useful for the treatment of osteoporosis and immune-related diseases such as organ transplant rejection and autoimmune diseases. Other exemplified thienodipyridine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
284486	Cl	Me	H	H	C ₂₂ H ₂₀ ClN ₃ O ₃ S
284487	Cl	Me	OMe	H	C ₂₃ H ₂₂ ClN ₃ O ₄ S
284488	Br	Me	H	H	C ₂₂ H ₂₀ BrN ₃ O ₃ S
284489	Cl	H	H	H	C ₂₁ H ₁₈ ClN ₃ O ₃ S
284490	Cl	Me	OMe	Ac	C ₂₅ H ₂₄ ClN ₃ O ₅ S
284491	Cl	H	OMe	Ac	C ₂₄ H ₂₂ ClN ₃ O ₅ S

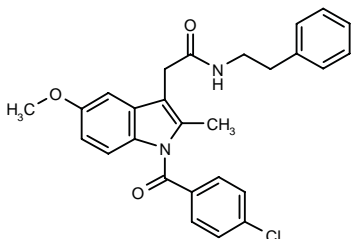
SOURCE – Takeda.

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1. Sohda, T. et al. (Takeda Chemical Industries, Ltd.) *Thienodipyridine derivs., production and use thereof*. WO 9965916.

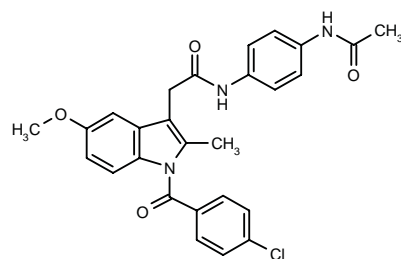
284747

2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-*N*-(2-phenylethyl)acetamide



C₂₇ H₂₅ Cl N₂ O₃; Mol wt: 460.9585

ACTION – Antiinflammatory agent, an amide derivative of indomethacin with potent and selective cyclooxygenase type 2 (COX-2)-inhibitory activity (IC₅₀ = 0.06 and > 66 μM for inhibition of COX-2 and COX-1, respectively); compound behaves as a slow, uncompetitive, tight-binding inhibitor of COX-2. It was able to inhibit COX-2 in intact cells, as demonstrated in RAW264.7 macrophages stimulated by lipopolysaccharide and interferon gamma (IC₅₀ = 0.04 μM), with activity comparable to indomethacin (IC₅₀ = 0.01 μM). Compound showed *in vivo* antiinflammatory activity in the carrageenan-induced paw edema test in rats and efficacy similar to indomethacin (ED₅₀ = 1.5 and 2 mg/kg p.o., respectively); unlike parent compound, this amide derivative is devoid of gastric ulcerogenic activity at up to 50 mg/kg p.o. No conversion of compound to indomethacin was detected in plasma or in rat liver and human liver microsomes. Another related compound is:



284745: C₂₇ H₂₄ Cl N₃ O₄

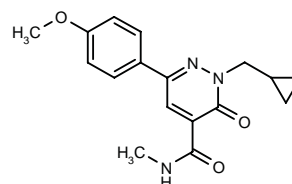
SOURCE – Vanderbilt University, Nashville, TN (US).

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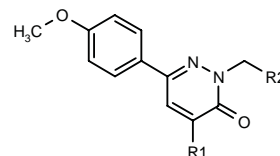
284821

2-(Cyclopropylmethyl)-6-(4-methoxyphenyl)-*N*-methyl-3-oxo-2,3-dihydropyridazine-4-carboxamide



C₁₇ H₁₉ N₃ O₃; Mol wt: 313.3551

ACTION – Agent for the treatment or prevention of immune, inflammatory and ischemic disorders, an inhibitor of the production of IL-1β (IC₅₀ = 0.038 μM in lipopolysaccharide-stimulated HL-60 cells). A representative compound from a series of pyridazine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
284822	CONHEt	cyclopropyl	C ₁₈ H ₂₁ N ₃ O ₃
284823	NHCO ₂ Et	(E)-4-Cl-PhCH=CH	C ₂₃ H ₂₂ ClN ₃ O ₄

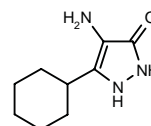
SOURCE – Kowa.

REFERENCES

1. Ohkuchi, M. et al. (Kowa Co., Ltd.) *Novel pyridazine derivs. and drugs containing the same as the active ingredient*. WO 9944995.

284840

4-Amino-5-cyclohexyl-2,3-dihydro-1*H*-pyrazol-3-one



C₉ H₁₅ N₃ O; Mol wt: 181.2375

ACTION – Agent for the treatment of inflammatory diseases, atherosclerosis, restenosis and immune disorders, especially those associated with the accumulation of lymphocytes or monocytes such as arthritis and transplant rejection, a monocyte chemoattractant protein-1 (MCP-1) antagonist ($IC_{50} = 1.27 \mu M$ against $[^{125}I]$ -MCP-1 binding in human monocytic THP-1 cell membranes). *In vitro*, compound produced 33-70% inhibition of MCP-1-induced chemotaxis of human T-lymphocyte blast cells at $10 \mu M$. In addition, it was found to be active in a streptococcal cell wall (SCW) arthritis model in rats following oral administration and was shown to inhibit the recruitment of T-cells in a cutaneous delayed hypersensitivity model in rats at 15 mg/kg p.o. A representative compound from a series of pyrazolone derivatives.

SOURCE – Warner-Lambert.

REFERENCES

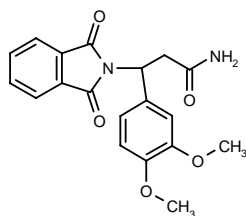
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CC-1069

269883

3-(3,4-Dimethoxyphenyl)-3-(1,3-dioxo-1,3-dihydro-2H-isindol-2-yl)propionamide

3-(3,4-Dimethoxyphenyl)-3-(phthalimido)propionamide



C19 H18 N2 O5; Mol wt: 354.3602

ACTION – Immunomodulator, an analogue of thalidomide and inhibitor of phosphodiesterase type 4 (PDE4; $IC_{50} = 9.4 \mu M$) proven to inhibit lipopolysaccharide (LPS)-induced TNF- α ($IC_{50} = 12.6 \mu M$), IL-1 β and IL-12 production and increase LPS-induced IL-10 production in human peripheral blood mononuclear cells, with little effect on T-cell activation. It was also more effective than thalidomide in inhibiting human umbilical vein endothelial cell (HUVEC) proliferation ($IC_{50} = 141 \mu M$ vs. $333 \mu M$). *In vivo* in the adjuvant-induced arthritis model in rats, compound (50-200 mg/kg/day i.p.) provided significant and long-lasting suppression of inflammatory synovitis and joint destruction as compared to placebo- or thalidomide-treated animals, as demonstrated by histological evidence of decreased inflammatory cell infiltration and reduced bone resorption; TNF- α and IL-2 levels in ankle joints were also lower in CC-1069-treated animals. Potentially useful for the treatment of chronic inflammatory diseases and angiogenesis-dependent tumors.

SOURCE – Celgene.

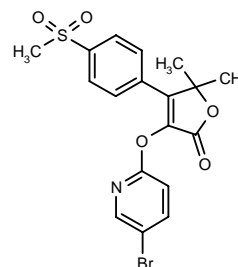
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5. Moreira, A.L. et al. *Thalidomide and thalidomide analogs reduce HIV type 1 replication in human macrophages in vitro*. AIDS Res Hum Retroviruses 1997, 13(10): 857.
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8. Oliver, S.J. et al. *Thalidomide analogue CC1069 inhibits development of rat adjuvant arthritis*. Clin Exp Immunol 1999, 118(2): 315.
9. Oliver, S.J. et al. *Thalidomide and analog CC1069 in rat adjuvant arthritis*. 62nd Annu Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 392.

L-778736

268021

3-(5-Bromopyridin-2-yloxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]furan-2(5H)-one



C18 H16 Br N O5 S; Mol wt: 438.2964

ACTION – Potent, selective and orally active cyclooxygenase type 2 (COX-2) inhibitor ($IC_{50} = 20$ and 30 nM , respectively, in CHO cells expressing human COX-2 and in human whole blood) with 180-280-fold selectivity over COX-1 ($IC_{50} = 5.6 \mu M$). Compound exhibited a good pharmacokinetic profile and excellent efficacy *in vivo*, as demonstrated in the rat paw edema assay ($ED_{50} = 0.86 \text{ mg/kg}$) and in rat models of pyrexia, hyperalgesia and adjuvant arthritis ($ED_{50} = 0.3, 0.6$ and 0.2 mg/kg , respectively). It was devoid of ulcerogenic activity at doses 100-fold higher than the doses required for antiinflammatory, analgesic and antipyretic effects. Potentially useful for the treatment of acute and chronic inflammatory diseases.

SOURCE – Merck & Co.

REFERENCES

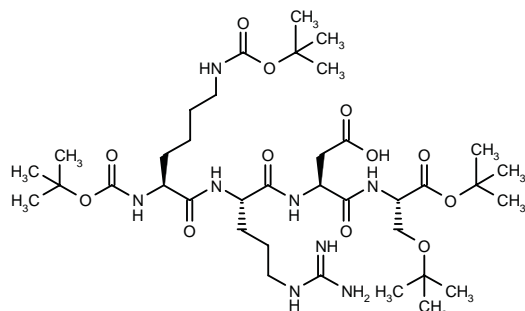
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PEP-1261

283567

*N*², *N*⁶-Bis(*tert*-butoxycarbonyl)-L-lysyl-L-arginyl-L-aspartyl-*O*-(*tert*-butyl)-L-serine *tert*-butyl ester



C37 H68 N8 O12; Mol wt: 816.9882

ACTION – Antiinflammatory agent, a tetrapeptide corresponding to a region of the *N*-terminal portion of lactotransferrin. Compound exhibited strong antiinflammatory activity in the acute carrageenan-induced paw inflammation model in rats, where it reduced paw volume and decreased enzyme levels, and in the subacute cotton pellet-induced granuloma model in rats, where it significantly inhibited the formation of granulation tissue and reduced enzyme levels in liver and exudate. In addition, at a dose of 15 mg/kg/day i.p. for 14 days it was associated with marked antiarthritic activity in the rat adjuvant-induced arthritis model, where it significantly reduced paw volume and decreased lysosomal enzyme levels. Further evaluation in models of carrageenan/arachidonic acid-, prostaglandin- and leukotriene-induced inflammation demonstrated that compound possesses antiinflammatory activity comparable to standard drugs such as diclofenac sodium and dexamethasone. *In vitro* studies showed its ability to inhibit the release of reactive oxygen species (H_2O_2 , O_2^-) and to reduce levels of myeloperoxidase and lysosomal enzymes from PMA-stimulated human neutrophils and neutrophils isolated from rats with adjuvant-induced arthritis. Moreover compound exhibited a membrane-stabilizing effect and significantly reduced gelatinase levels in bone homogenates.

SOURCE – Central Leather Research Institute, Madras (IN).

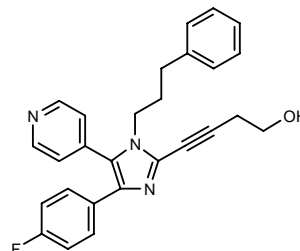
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RWJ-67657*

270783

4-[4-(4-Fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1*H*-imidazol-2-yl]-3-butyne-1-ol



C27 H24 F N3 O; Mol wt: 425.5046

ACTION – p38 MAP kinase inhibitor able to inhibit lipopolysaccharide (LPS)-induced TNF- α and IL-1 β production in human peripheral blood mononuclear cells (PBMCs; IC_{50} = 3 and 11 nM, respectively), as well as TNF- α release from PBMCs stimulated by staphylococcal enterotoxin B (IC_{50} = 13 nM); the standard reference compound SB-203580 had 10-fold higher IC_{50} values in these assays. Compound was seen to inhibit the enzymatic activity of recombinant p38 α and p38 β , but not p38 γ or p38 δ , and it had no significant activity against a variety of other enzymes, whereas SB-203580 had significant inhibitory activity against p56lck and c-src tyrosine kinases. *In vivo*, compound given orally was able to strongly inhibit LPS-induced TNF- α production in both mice (87% inhibition at 50 mg/kg) and rats (91% inhibition at 25 mg/kg). It is currently undergoing further preclinical evaluation as a potential treatment for rheumatoid arthritis, endotoxic shock, inflammatory bowel disease and osteoporosis.

SOURCES – Ortho-McNeil; R.W. Johnson.

REFERENCES

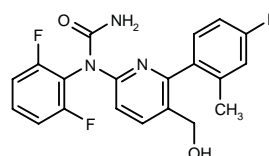
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- Wadsworth, S.A. et al. *RWJ 67657, a potent, orally active inhibitor of p38 mitogen-activated protein kinase*. *J Pharmacol Exp Ther* 1999, 291(2): 680.

*Identified compound **270783** Drug Data Rep 1999, 021(01): 0071.

VRT-37742

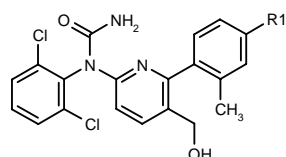
283673

N-(2,6-Difluorophenyl)-*N*-[6-(4-fluoro-2-methylphenyl)-5-(hydroxymethyl)pyridin-2-yl]urea



C20 H16 F3 N3 O2; Mol wt: 387.3594

ACTION – An inhibitor of mitogen-activated protein (MAP) kinase p38, with potential in the treatment of diseases mediated or exacerbated by the cytokines IL-1, TNF, IL-6 or IL-8 such as osteoarthritis, rheumatoid arthritis, osteoporosis, acute pancreatitis, asthma and a wide range of other inflammatory or autoimmune diseases. *In vitro*, compound inhibited p38 kinase, IL-1 and TNF production in lipopolysaccharide-stimulated human peripheral blood mononuclear cells (PBMCs), and IL-1, TNF and IL-6 production in whole blood with IC₅₀ values of 0.027, 0.027, 0.01, 0.057, 0.09 and 0.075 μ M, respectively. Other exemplified heterocyclic compounds include the following:



Compound	R1	Formula
VRT-032884 [283674]	H	C ₂₀ H ₁₇ Cl ₂ N ₃ O ₂
VRT-034465 [283675]	F	C ₂₀ H ₁₆ Cl ₂ FN ₃ O ₂

SOURCE – Vertex.

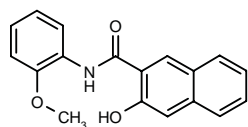
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1. Salituro, F. et al. (Vertex Pharmaceuticals Inc.) *Heterocyclic inhibitors of p38*. WO 9958502.

IMMUNOMODULATING AGENTS

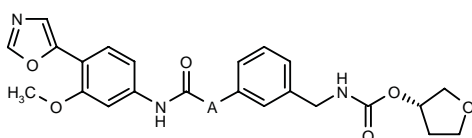
282695

3-Hydroxy-*N*-(2-methoxyphenyl)naphthalene-2-carboxamide

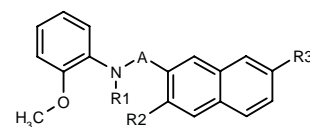


C₁₈ H₁₅ N O₃; Mol wt: 293.3205

ACTION – IMP (inosine-5'-monophosphate) dehydrogenase (IMPDH) inhibitor ($K_i < 10 \mu$ M) claimed for the treatment or prevention of transplant rejection, graft-versus-host disease, autoimmune diseases, hyperproliferative vascular diseases such as restenosis, cancer and inflammation, as well as for inhibiting viral replication. Other exemplified compounds include the following:



Compound	A	Formula
282698	CH ₂	C ₂₄ H ₂₅ N ₃ O ₆
282704	O	C ₂₃ H ₂₃ N ₃ O ₇



Compound	R1	R2	R3	A	Formula
282705	Me	OH	Br	CO	C ₁₉ H ₁₆ BrNO ₃
282706	H	H	H	SO ₂	C ₁₇ H ₁₅ NO ₃ S

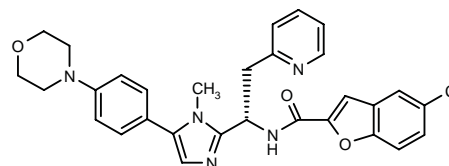
SOURCE – Vertex.

REFERENCES

1. Saunders, J. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of IMPDH enzyme*. WO 9955663.

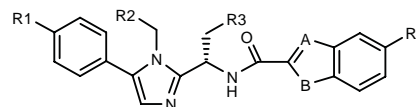
283046

5-Chloro-*N*-[1(*S*)-[1-methyl-5-[4-(4-morpholinyl)phenyl]-1*H*-imidazol-2-yl]-2-(pyridin-2-yl)ethyl]-1-benzofuran-2-carboxamide



C₃₀ H₂₈ Cl N₅ O₃; Mol wt: 542.0362

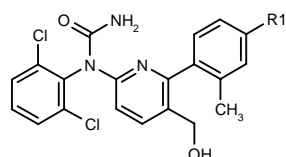
ACTION – Agent for the treatment of adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, heart failure, septic shock, diabetes, inflammatory bowel disease, cerebral infarction, rheumatoid arthritis, transplant rejection and other nitric oxide (NO)-mediated diseases that acts by inhibiting the production of NO, as demonstrated in the murine macrophage cell line RAW 264.7 (100% inhibition at 10 μ M). In addition, compound exerted a marked prolongation of rat cardiac allograft survival when given in combination with the immunosuppressive agent FK-506, with a median survival time (MST) of > 30 days when administered at 10 mg/kg + 0.32 mg/kg FK-506 intragastrically for 14 days compared to an MST of only 10 days for animals receiving FK-506 alone. A representative compound within a series of heterocyclic carboxamide derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	A	B	Formula
283052	Ph	H	2-Pyr	Br	CH	O	C ₃₂ H ₂₅ BrN ₄ O ₂
283061	1-imidazolyl	H	2-Pyr	H	CH	S	C ₂₉ H ₂₄ N ₆ OS
283065	1-imidazolyl	H	2-Pyr	NO ₂	CH	S	C ₂₉ H ₂₃ N ₇ O ₃ S
283067	1-imidazolyl	Me	4-Pyr	H	CH	NH	C ₃₀ H ₂₇ N ₇ O
283068	NO ₂	H	2-Pyr	OMe	CH	O	C ₂₇ H ₂₃ N ₅ O ₅
283069	1-imidazolyl	H	2-Pyr	H	N	S	C ₂₈ H ₂₃ N ₇ OS

SOURCE – Fujisawa.

ACTION – An inhibitor of mitogen-activated protein (MAP) kinase p38, with potential in the treatment of diseases mediated or exacerbated by the cytokines IL-1, TNF, IL-6 or IL-8 such as osteoarthritis, rheumatoid arthritis, osteoporosis, acute pancreatitis, asthma and a wide range of other inflammatory or autoimmune diseases. *In vitro*, compound inhibited p38 kinase, IL-1 and TNF production in lipopolysaccharide-stimulated human peripheral blood mononuclear cells (PBMCs), and IL-1, TNF and IL-6 production in whole blood with IC₅₀ values of 0.027, 0.027, 0.01, 0.057, 0.09 and 0.075 μ M, respectively. Other exemplified heterocyclic compounds include the following:



Compound	R1	Formula
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VRT-034465 [283675]	F	C ₂₀ H ₁₆ Cl ₂ FN ₃ O ₂

SOURCE – Vertex.

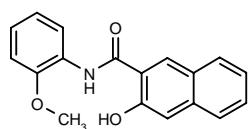
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1. Salituro, F. et al. (Vertex Pharmaceuticals Inc.) *Heterocyclic inhibitors of p38*. WO 9958502.

IMMUNOMODULATING AGENTS

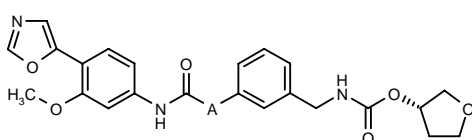
282695

3-Hydroxy-*N*-(2-methoxyphenyl)naphthalene-2-carboxamide

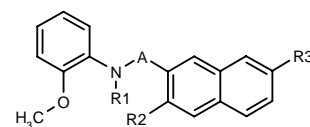


C₁₈ H₁₅ N O₃; Mol wt: 293.3205

ACTION – IMP (inosine-5'-monophosphate) dehydrogenase (IMPDH) inhibitor ($K_i < 10 \mu$ M) claimed for the treatment or prevention of transplant rejection, graft-versus-host disease, autoimmune diseases, hyperproliferative vascular diseases such as restenosis, cancer and inflammation, as well as for inhibiting viral replication. Other exemplified compounds include the following:



Compound	A	Formula
282698	CH ₂	C ₂₄ H ₂₅ N ₃ O ₆
282704	O	C ₂₃ H ₂₃ N ₃ O ₇



Compound	R1	R2	R3	A	Formula
282705	Me	OH	Br	CO	C ₁₉ H ₁₆ BrNO ₃
282706	H	H	H	SO ₂	C ₁₇ H ₁₅ NO ₃ S

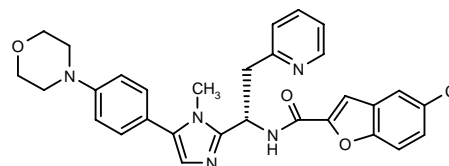
SOURCE – Vertex.

REFERENCES

1. Saunders, J. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of IMPDH enzyme*. WO 9955663.

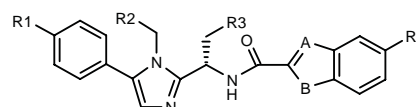
283046

5-Chloro-*N*-[1(*S*)-[1-methyl-5-[4-(4-morpholinyl)phenyl]-1*H*-imidazol-2-yl]-2-(pyridin-2-yl)ethyl]-1-benzofuran-2-carboxamide



C₃₀ H₂₈ Cl N₅ O₃; Mol wt: 542.0362

ACTION – Agent for the treatment of adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, heart failure, septic shock, diabetes, inflammatory bowel disease, cerebral infarction, rheumatoid arthritis, transplant rejection and other nitric oxide (NO)-mediated diseases that acts by inhibiting the production of NO, as demonstrated in the murine macrophage cell line RAW 264.7 (100% inhibition at 10 μ M). In addition, compound exerted a marked prolongation of rat cardiac allograft survival when given in combination with the immunosuppressive agent FK-506, with a median survival time (MST) of > 30 days when administered at 10 mg/kg + 0.32 mg/kg FK-506 intragastrically for 14 days compared to an MST of only 10 days for animals receiving FK-506 alone. A representative compound within a series of heterocyclic carboxamide derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	A	B	Formula
283052	Ph	H	2-Pyr	Br	CH	O	C ₃₂ H ₂₅ BrN ₄ O ₂
283061	1-imidazolyl	H	2-Pyr	H	CH	S	C ₂₉ H ₂₄ N ₆ OS
283065	1-imidazolyl	H	2-Pyr	NO ₂	CH	S	C ₂₉ H ₂₃ N ₇ O ₃ S
283067	1-imidazolyl	Me	4-Pyr	H	CH	NH	C ₃₀ H ₂₇ N ₇ O
283068	NO ₂	H	2-Pyr	OMe	CH	O	C ₂₇ H ₂₃ N ₅ O ₅
283069	1-imidazolyl	H	2-Pyr	H	N	S	C ₂₈ H ₂₃ N ₇ OS

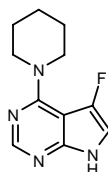
SOURCE – Fujisawa.

REFERENCES

1. Shima, I. et al. (Fujiwara Pharmaceutical Co., Ltd.) *Heterocyclic carboxamide derivs. as inhibitors of nitric oxide production*. WO 9957114.

284523

5-Fluoro-4-(piperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine



C11 H13 F N4; Mol wt: 220.2497

ACTION – Immunosuppressive agent that inhibits Janus kinase 3 (JAK3), the expression of which is limited to hematopoietic cells and which appears to play a critical role in B- and T-cell maturation and the maintenance of T-cell function. As such, the compound is expected to be of utility for organ transplants, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, type I diabetes and diabetic complications, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other autoimmune diseases. Other specifically claimed pyrrolo[2,3-d]pyrimidine compounds include the following:



Compound	R1	R2	R3	Formula
284524	2-Et-4-[C(Me)2OH]-cyclopentyl	OH	H	C ₁₈ H ₂₈ N ₄ O ₂
284527	-(CH ₂) ₃ -		3-[N(Me)2CH2CH2-NHCH2]-Ph	C ₂₂ H ₃₀ N ₆
284532	-(CH ₂) ₃ -		3-i-Pr-Ph	C ₂₀ H ₂₄ N ₄
284533	-(CH ₂) ₃ -		1-Me-5-imidazolyl	C ₁₅ H ₁₈ N ₆
284535	-(CH ₂) ₃ -		Cl	C ₁₁ H ₁₃ ClN ₄
284536	-CH ₂ C(Me)2CH ₂ -		H	C ₁₃ H ₁₈ N ₄

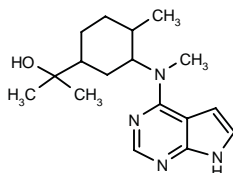
SOURCE – Pfizer.

REFERENCES

1. Blumenkopf, T.A. et al. (Pfizer Products Inc.) *Pyrrolo[2,3-d]pyrimidine cpds*. WO 9965909.

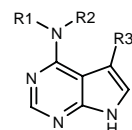
284549

2-[4-Methyl-3-[N-methyl-N-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)cyclohexyl]propan-2-ol

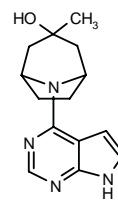


C17 H26 N4 O; Mol wt: 302.4194

ACTION – Immunosuppressive agent that inhibits Janus kinase 3 (JAK3), the expression of which is limited to hematopoietic cells and which appears to play a critical role in B- and T-cell maturation and the maintenance of T-cell function. As such, this compound is expected to be of utility for organ transplants, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, type I diabetes and diabetic complications, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other autoimmune diseases. Other specifically claimed pyrrolo[2,3-d]pyrimidine compounds include the following:



Compound	R1	R2	R3	Formula
284552	CH ₂ CH ₂ OH	2-Me-5-[CH ₂ =C(Me)]-cyclohexyl	H	C ₁₈ H ₂₆ N ₄ O
284553	CH ₂ CF ₃	2-Me-5-[C(Me)2OH]-cyclohexyl	H	C ₁₈ H ₂₆ F ₃ N ₄ O
284554		-CH[C(Me)2OH]CH ₂ CH ₂ -	H	C ₁₂ H ₁₆ N ₄ O
284555	Me	2-Me-5-[C(Me)2OH]-cyclohexyl	F	C ₁₇ H ₂₅ FN ₄ O
284557	cyclooctyl	CH ₂ CH ₂ OH	H	C ₁₆ H ₂₄ N ₄ O



284556: C₁₄ H₁₈ N₄ O

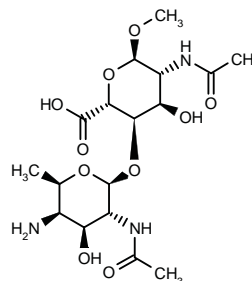
SOURCE – Pfizer.

REFERENCES

1. Blumenkopf, T.A. et al. (Pfizer Products Inc.) *Pyrrolo[2,3-d]pyrimidine cpds*. WO 9965908.

284567

4-O-(2-Acetamido-4-amino-2,4,6-trideoxy-β-D-galactopyranosyl)-2-acetamido-2-deoxy-1-O-methyl-α-L-altropyranosuronic acid



C17 H29 N3 O10; Mol wt: 435.4271

ACTION – Zwitterionic disaccharide that corresponds to the repeating unit of O-specific polysaccharide of the Gram-negative human pathogen *Shigella sonnei*. Antigenicity was demonstrated in the *S. sonnei* passive hemolysis inhibition test (IC₅₀ = 3.9 mM). Potentially useful as a component of a vaccine for enteric diseases.

SOURCES – Hungarian Academy of Sciences, Budapest (HU); National Institutes of Health, Bethesda, MD (US).

REFERENCES

1. Tóth, A. et al. *Synthesis of the repeating unit of the O-specific polysaccharide of Shigella sonnei and quantitation of its serologic activity*. Bioorg Med Chem Lett 2000, 10(1): 19.

CABIN 1

284606

ACTION – Polypeptide that binds to calcineurin and inhibits calcineurin function including the interaction between calcineurin and NF-AT, thus inhibiting transcriptional activation of calcineurin-responsive genes such as IL-2, IL-3, IL-4, TNF- α and interferon gamma. Potentially useful as an immunosuppressive agent.

SOURCE – Massachusetts Institute of Technology, Cambridge, MA (US).

REFERENCES

1. Liu, J.O. et al. (Massachusetts Institute of Technology) *Immunosuppressive agents that inhibit calcineurin function and uses thereof*. WO 9965450.

LPD-LB1(f)_{2,1,3}

284521

Chimeric polypeptide comprising three different P5-like fimbria subunit peptides (also called LB1(f) peptides) of P5-like fimbria proteins from various nontypeable Haemophilus influenzae (ntHi) strains and lipoprotein D

ACTION – Chimeric polypeptide for use as an immunogenic agent in the preparation of vaccines for the treatment or prevention of *Haemophilus influenzae* diseases such as otitis media, sinusitis, conjunctivitis and lower respiratory tract infection. Efficacy was shown in a chinchilla model of nontypeable *H. influenzae* (ntHi)-caused otitis media induced by successive intranasal administration of adenovirus and ntHi.

SOURCES – Ohio State University, Columbus, OH (US); SmithKline Beecham.

REFERENCES

1. Bakaletz, L.O. et al. (Ohio State University; SmithKline Beecham Biologicals SA) *Vaccine*. WO 9964067.
2. Bakaletz, L.O. et al. *Protection against development of otitis media induced by nontypeable Haemophilus influenzae by both active and passive immunization in a chinchilla model of virus-bacterium superinjection*. Infect Immun 1999, 67(6): 2746.

TA-GW PHARMACCINE*

202922

Vaccine comprising the recombinant protein L2E7, a fusion of the L2 and E7 proteins of human papillomavirus (HPV), formulated with the adjuvant SBAS2

TH-GW pharmaccine
TA-GW

ACTION – Therapeutic vaccine for genital warts, a fusion protein consisting of human papillomavirus (HPV6) L2E7 and originally formulated with the adjuvant Alhydrogel®. A phase II study in 27 subjects with genital warts demonstrated that it is safe and well tolerated and immunogenic; all subjects produced serum IgG antibodies against L2E7 and 75% of patients generated an antigen-specific T-cell proliferative response to L2E7. When peripheral mononuclear cells derived from vaccinated individuals were treated *in vitro* with L2E7, they produced both interferon gamma and IL-5, IL-5 predominating after the final vaccination. Preliminary encouraging responses were noted in this study, in which 5 patients treated with the vaccine alone had complete clearance of warts within 8 weeks. Phase IIB studies are in progress using the HPV6 L2E7 immunogen adjuvanted with SBAS2.

SOURCES – Cantab; SmithKline Beecham.

REFERENCES

1. Whittle, N.R. et al. (Cantab Pharmaceuticals plc) *Polypeptides useful as immunotherapeutic agents and methods of polypeptide preparation*. US 5955087.
2. Lacey, C.J.N. et al. *Phase IIa safety and immunogenicity of a therapeutic vaccine, TA-GW, in persons with genital warts*. J Infect Dis 1999, 179(3): 612.
3. Thompson, H.S. et al. *Enhanced immunogenicity of a recombinant genital warts vaccine adjuvanted with monophosphoryl lipid A*. Vaccine 1998, 16(20): 1993.
4. Thompson, H.S.G. et al. *Phase I safety and antigenicity of TA-GW: A recombinant HPV6 L2E7 vaccine for the treatment of genital warts*. Vaccine 1999, 17(1): 40.
5. *Cantab and SmithKline Beecham form vaccine collaboration*. Cantab Pharmaceuticals plc Press Release 1996, July 18.
6. *Cantab highlights achievements in development programs during Q2 1999*. DailyDrugNews.com (Daily Essentials) 1999, Aug 4.
7. *Cantab makes steady progress during 1999*. DailyDrugNews.com (Daily Essentials) 2000, Feb 23.
8. *Cantab's therapeutic vaccine for genital warts enters phase II trials*. DailyDrugNews.com (Daily Essentials) 1999, July 20.
9. *Safety, immunogenicity and proof of principle with TA-GW*. Cantab Pharmaceuticals plc Press Release 1996, Nov 29.
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12. Cantab Pharmaceuticals plc Annual Report 1995.

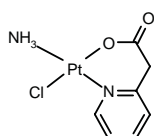
*Identified compound **202922** (see **TA-HPV**) Drug Data Rep 1994, 016(01): 0071.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

284140

trans-[(Ammine(chloro)[2-(2-pyridinyl-κN)acetato-κO](-1))]platinum



C7 H9 Cl N2 O2 Pt; Mol wt: 383.6931

ACTION – Antineoplastic agent, a water-soluble *trans*-platinum complex with comparable *in vitro* cytotoxicity to cisplatin against murine leukemia L1210 cells ($ID_{50} = 0.88 \mu M$ vs. $0.43 \mu M$ for cisplatin) and superior activity as compared to the corresponding *cis*-isomer ($ID_{50} > 20 \mu M$) and transplatin ($ID_{50} = 14 \mu M$).

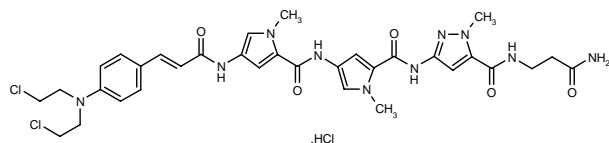
SOURCE – Virginia Commonwealth University, Richmond, VA (US).

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1. Farrell, N.P. and Bierbach, U. (Virginia Commonwealth University) *Water soluble transplatinum complexes with anti-cancer activity and method of using same*. US 6001872.

284316

N-(2-Carbamoyl-ethyl)-3-[4-[4-[3-[4-[*N,N*-bis(2-chloro-ethyl)amino]phenyl]-2(*E*)-propenamido]-1-methyl-1*H*-pyrrol-2-ylcarboxamido]-1-methyl-1*H*-pyrrol-2-ylcarboxamido]-1-methyl-1*H*-pyrazole-5-carboxamide hydrochloride



C33 H38 Cl2 N10 O5 . HCl; Mol wt: 762.0951

ACTION – Antineoplastic agent, a representative compound from a series of cinnamoyl derivatives of distamycin A acting as alkylating agents and reported to have activity *in vitro* and *in vivo* against murine leukemia L1210 cells.

SOURCE – Pharmacia & Upjohn (Pharmacia).

REFERENCES

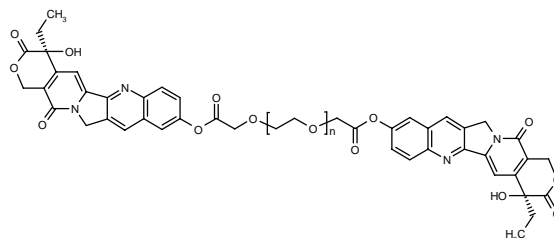
1. Cozzi, P. et al. (Pharmacia & Upjohn SpA) *Cinnamoyl distamycin analogous derivs., process for their preparation, and their use as antitumor agents*. WO 9964413.

DNA-INTERCALATING DRUGS

284842

Poly(ethyleneglycol)-1,3^o-dicarboxylic acid camptothecin-10-yl diester

Poly(ethyleneglycol)-1,3^o-dicarboxylic acid bis[4(*S*)-ethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-9-yl]diester



ACTION – Antineoplastic agent, a polyethylene glycol (PEG)-conjugated camptothecin that acts as a water-soluble prodrug of the latter, with improved efficacy both *in vitro* and *in vivo*. Cytotoxic activity was demonstrated against murine leukemia P388/0 cells, with an IC_{50} value of 55 nM versus 139 nM for 10-hydroxycamptothecin. When tested *in vivo* in mice bearing murine P388/0 leukemia, compound was more effective than topotecan in prolonging survival of animals (ILS = 173% vs. 92% for topotecan, both at 16 mg/kg/day i.p. x 5 days).

SOURCE – Enzon.

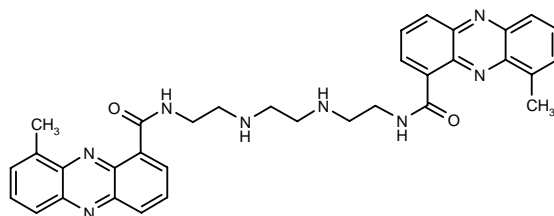
REFERENCES

1. Greenwald, R.B. et al. (Enzon, Inc.) *Acyl polymeric derivs. of aromatic hydroxyl-containing cpds*. US 6011042.

XR-5944

274523

N,N'-(1,2-Ethanediy)bis(imino-2,1-ethanediy)bis(9-methylphenazine-1-carboxamide)



C34 H34 N8 O2; Mol wt: 586.6966

ACTION – Antineoplastic agent, an inhibitor of both topoisomerase I and II with preferential effects on topoisomerase I. Compound exhibited potent cytotoxicity *in vitro* against human tumor cells including small cell lung cancer H69 ($IC_{50} = 0.4$ nM), non-small cell lung cancer COR-L23 ($IC_{50} = 0.04$ nM), Jurkat leukemia ($IC_{50} = 0.09$ nM) and colon HT29 cells ($IC_{50} = 1.4$ nM), as well as against multidrug resistance protein (MRP1)- and P-glycoprotein (P-gp)-expressing cell lines ($IC_{50} = 0.3$ -155 nM). It retained significant activity in cell lines expressing atypical drug resistance including amsacrine-resistant or doxorubicin-resistant Jurkat leukemia cells ($IC_{50} = 0.054$ and 0.063 nM, respectively) and camptothecin-resistant DC3F Chinese hamster lung cells ($IC_{50} = 4$ nM). Antitumor efficacy was observed *in vivo* in both syngeneic (colon 38) and xenograft (small cell lung H69 and colon HT29) models. In particular, in the resistant human colon tumor HT29 xenograft model, compound (15 mg/kg i.v. every 4 days x 3) produced tumor stasis during the treatment period and a longer tumor growth delay than doxorubicin or TAS-103; in the human small cell lung cancer H69 xenograft model, it induced complete tumor regression at 10-15 mg/kg i.v. every 4 days x 3.

SOURCE – Xenova.

REFERENCES

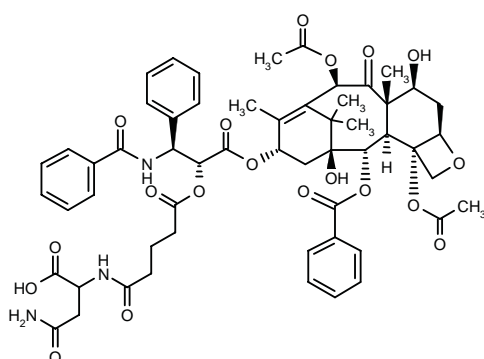
1. Denny, W.A. et al. (Xenova Group plc) *Bis(acridinecarboxamide) and bis(phenazinecarboxamide) as antitumour agents*. EP 0934278, GB 2334032, WO 9817650.
2. Stewart, A.J. et al. *Antitumour activity of XR5944, a novel topoisomerase inhibitor*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 675.
3. Stewart, A.J. et al. *Evaluation of a novel potent topoisomerase inhibitor, XR5944*. Proc Amer Assoc Cancer Res 1999, 40: Abst 764.

ANTIMITOTIC DRUGS

282538

2'-O-[4-[N-(1-Carboxy-2-carbamoyl)ethyl]carbamoyl]butyryl]paclitaxel

[2aR,4aS,4aS,6R,9S(2'R,3'S),11S,12S,12aR,12bS]-6,12b-Diacetoxy-8-[3-benzamido-2-[4-[N-(1-carboxy-2-carbamoyl)ethyl]carbamoyl]butyryloxy]-3-phenylpropionyloxy]-12-benzoyloxy-4,11-dihydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benz[1,2-b]oxet-5-one



C56 H63 N3 O19; Mol wt: 1082.1160

ACTION – Antineoplastic agent, a paclitaxel derivative with improved water solubility but somewhat lower cytotoxicity, as shown by relative ratios (IC_{50} compound/ IC_{50} paclitaxel) of 7.9, 3.3, 18.9 and 12.8 when tested against ovarian teratocarcinoma CRL-1572, prostate carcinoma LNCaP, murine melanoma B16 and murine fibroblast 3T3 cells, respectively.

SOURCE – Laval University, Quebec (CA).

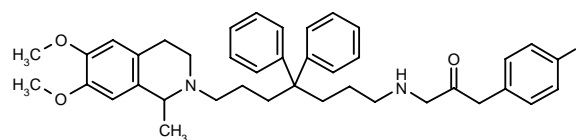
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1. Pagé, M. et al. (Laval University) *Water-soluble derivs. of paclitaxel, method for producing same and uses thereof*. US 5981564, WO 0001682.

HORMONAL AGENTS

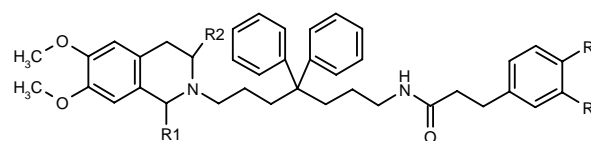
282559

1-(4-Fluorophenyl)-3-[7-(6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-4,4-diphenylheptylamino]propan-2-one



C40 H47 F N2 O3; Mol wt: 622.8203

ACTION – Luteinizing hormone-releasing hormone (LHRH) antagonist with a pK_i value of 11.64 in a rat pituitary LHRH receptor binding assay, potentially useful in the treatment of a variety of sex hormone-related conditions such as precocious puberty, benign prostatic hyperplasia, breast and ovarian cancer, prostate cancer, gastric motility disorders, dysmenorrhea and endometriosis. A representative compound from a series of tetrahydroisoquinoline derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
282560	4-NH2-PhCH2	H	F	H	C ₄₆ H ₅₂ FN ₃ O ₃
282561	cyclopropyl-CH2NH(CH2)4	H	F	H	C ₄₇ H ₆₀ FN ₃ O ₃
282562	Me	Me	F	H	C ₄₁ H ₄₈ FN ₂ O ₃
282564	Me	H	F	F	C ₄₀ H ₄₆ F ₂ N ₂ O ₃
282565	Me	H	Cl	F	C ₄₀ H ₄₆ ClFN ₂ O ₃

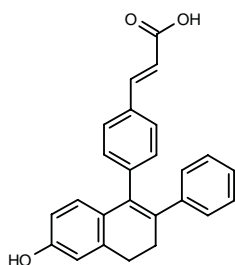
SOURCE – Abbott.

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1. Haviv, F. et al. (Abbott Laboratories Inc.) *Tetrahydroisoquinoline derivs. as LHRH antagonists*. US 5981521.

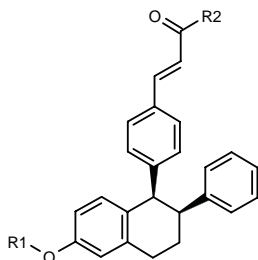
282783

3-[4-(6-Hydroxy-2-phenyl-3,4-dihydronaphthalen-1-yl)-phenyl]-2-propenoic acid



C25 H20 O3; Mol wt: 368.4300

ACTION – Agent for the treatment and/or prevention of osteoporosis, breast cancer and menopausal symptoms that exerts estrogenic effects on the bone while exhibiting minimal activity on the uterus and no endometrial proliferative activity; it also exerts antiestrogenic and/or antiproliferative effects on breast tissue. Compound exhibited a relative binding affinity for the human estrogen receptor of 72% (estradiol = 100%) using cytosolic extracts of SF9 cells containing recombinant human receptors. In addition, compound was shown to inhibit the proliferation of human mammary tumor MCF-7 cells. Other compounds from this series of dihydro- and tetrahydronaphthalene derivatives include the following:



Compound	R1	R2	Isomer	Formula
282784	H	OH	(±)-cis	C ₂₅ H ₂₂ O ₃
282785	Me	N(Et)2	(±)-cis	C ₃₀ H ₃₃ NO ₂
282786	H	N(Et)2	(±)-cis	C ₂₉ H ₃₁ NO ₂

SOURCE – Aventis Pharma.

REFERENCES

1. Nique, F. (Hoechst Marion Roussel, SA) *Dihydro- or tetrahydronaphthalene derivs. having (anti-)estrogen activity*. EP 0955286, FR 2778404, JP 1999349527, US 6005003.

ACTION – Antiestrogenic agent proven to inhibit the 17β-estradiol benzoate-induced increase in uterine weight of ovariectomized mice both following s.c. (51.0% inhibition at 30 μg/day x 3 days) and p.o. administration (81.3% inhibition at 10 mg/kg/day x 3 days). *In vitro*, compound inhibited the growth of MCF-7 cells with an IC₅₀ value of 850.5 nM.

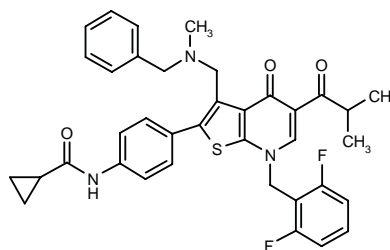
SOURCE – C & C Research.

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1. Joe, J.C. et al. (C & C Research Laboratories) *Novel benzopyran or thiobenzopyran derivs.* WO 9965893.

284697

N-[4-[3-(*N*-Benzyl-*N*-methylaminomethyl)-7-(2,6-difluorobenzyl)-5-(2-methylpropionyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridin-2-yl]phenyl]cyclopropanecarboxamide



C37 H35 F2 N3 O3 S; Mol wt: 639.7635

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist shown to inhibit [¹²⁵I]-leuporelin binding in rat pituitary anterior lobe membranes and in CHO cells expressing the human GnRH receptor with IC₅₀ values of 0.06 and 0.0001 μM, respectively. Compound also significantly suppressed plasma luteinizing hormone (LH) levels in castrated male cynomolgus monkeys at 30 mg/kg p.o. Potentially useful in the treatment of sex hormone-dependent disorders such as sex hormone-dependent cancer, prostatic hypertrophy, endometriosis, precocious puberty, amenorrhea, infertility and for regulating pregnancy and menstruation.

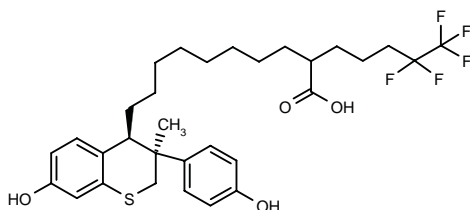
SOURCE – Takeda.

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284614

(±)-*trans*-10-[7-Hydroxy-3-(4-hydroxyphenyl)-3-methyl-3,4-dihydro-2*H*-1-benzothiopyran-4-yl]-2-(4,4,5,5,5-pentafluoropentyl)decanoic acid



C31 H39 F5 O4 S; Mol wt: 602.7011

CANCER IMMUNOTHERAPY

GEMTUZUMAB ZOGAMICIN

198455

Humanized IgG₄ anti-CD33 antibody hP67.6 conjugated to N-acetyl-γ-calicheamicin DMH, with a bifunctional AcBut linker

CDP-771
CMA-676
Mylotarg™

ACTION – Antineoplastic agent, an immunoconjugate consisting of an anti-CD33 antibody linked to the cytotoxic antibiotic calicheamicin. Compound showed excellent *in vitro* activity and selectivity and a broad therapeutic window. In a phase II trial in patients with acute myeloid leukemia (AML) in first relapse, at a dose of 9 mg/m² i.v. every 2 weeks x 2 it induced remission in 43% of the patients with acceptable safety. It also induced selective ablation of malignant hematopoiesis in some patients with relapsed or refractory CD33+ AML. Compound is under review at the FDA for the treatment of CD33+ AML in relapse.

SOURCES – Celltech Chiroscience (Celltech Group); Wyeth-Ayerst.

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20. *Preliminary results indicate potential for AML treatment.* DailyDrugNews.com (Daily Essentials) 1997, May 21.

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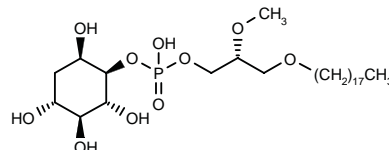
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INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

268094

Phosphoric acid 2(R)-methoxy-3-octadecyloxypropyl 1(R),2(R),3(S),4(R),6(R)-tetrahydroxycyclohexyl diester



C28 H57 O10 P; Mol wt: 584.7223

ACTION – Antineoplastic agent, an inhibitor of phosphatidylinositol 3-kinase (IC₅₀ = 2.5 μM) with weak inhibitory activity against phosphatidylinositol-specific phospholipase C hydrolysis (IC₅₀ = 19.9 μM). Compound showed high cytotoxicity against human colon adenocarcinoma HT-29 cells (IC₅₀ = 2.1 μM) *in vitro* and was able to reduce the growth of such tumors implanted s.c. in SCID mice (67% inhibition at 150 mg/kg/day i.p.).

SOURCE – Georgetown University, Washington, DC (US).

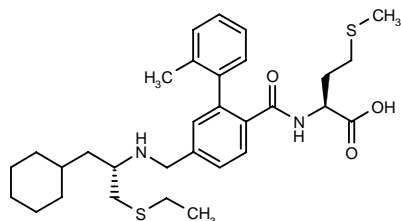
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283265

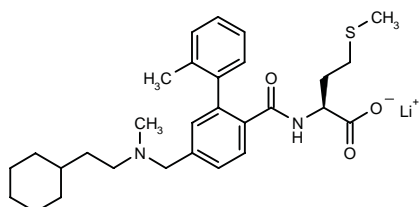
2(S)-[5-[2-Cyclohexyl-1(S)-(ethylsulfanylmethyl)ethylaminomethyl]-2'-methylbiphenyl-2-ylcarboxamido]-4-(methylsulfanyl)butyric acid

N-[5-[2-Cyclohexyl-1(S)-(ethylsulfanylmethyl)ethylaminomethyl]-2'-methylbiphenyl-2-ylcarbonyl]-L-methionine



C31 H44 N2 O3 S2; Mol wt: 556.8316

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase ($IC_{50} = 0.20$ nM) that is able to inhibit Ras prenylation in whole cells ($EC_{50} = 4.4$ nM). In nude mice bearing human pancreatic cancer MiaPaCa xenografts, compound reduced tumor size by 54% relative to untreated controls at a dose of 100 mg/kg/day p.o. Another compound within this series of peptidomimetic cyclohexylethylamine-containing inhibitors is:



283264: C29 H39 Li N2 O3 S

SOURCES – Abbott; University of Pittsburgh, Pittsburgh, PA (US).

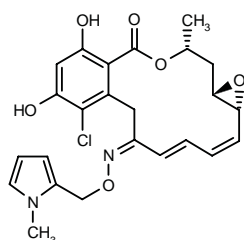
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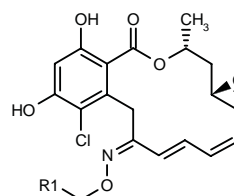
283685

(1*aR*,14*R*,15*aS*)-8-Chloro-9,11-dihydroxy-14-methyl-6,7,12,14,15,15a-hexahydro-1*aH*-oxireno[2,3-*e*]-2-benzoxacyclotetradecine-6,12-dione 6-[*O*-(1-methyl-1*H*-pyrrol-2-ylmethyl)oxime]



C24 H25 Cl N2 O6; Mol wt: 472.9225

ACTION – Antineoplastic and immunosuppressive agent with tyrosine kinase-inhibitory activity ($IC_{50} = 0.06$ μ M in SR-3Y1 cells). Antiproliferative activity was demonstrated preferentially against *v-src*-transformed rat fibroblast SR-3Y1 cells ($IC_{50} = 0.009$ μ M) compared to untransformed rat fibroblasts ($IC_{50} = 0.056$ μ M). *In vivo*, compound showed antitumor activity against human breast carcinoma MX-1 xenografts in nude mice, giving a T/C value of 31% at 100 mg/kg/day i.v. x 5 days. A representative compound from a series of radicicol derivatives, wherein the following are also included:



Compound	R1	Formula
283686	4-Pyr-CH2NH(CH2)3	C ₂₈ H ₃₂ ClN ₃ O ₆
283687	(CH2)3NHCONHMe	C ₂₄ H ₃₀ ClN ₃ O ₇
283688	1-Me-2-imidazolyl	C ₂₃ H ₂₄ ClN ₃ O ₆
283689	2-pyrazinyl	C ₂₃ H ₂₂ ClN ₃ O ₆
283690	2-oxo-3-oxazolidinyl-CH2	C ₂₃ H ₂₅ ClN ₂ O ₈
283691	2-oxo-1-Pip-CH2	C ₂₅ H ₂₉ ClN ₂ O ₇

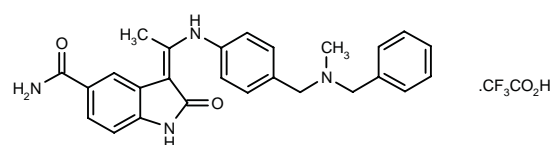
SOURCE – Kyowa Hakko.

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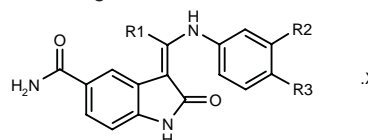
284233

3-[(*Z*)-1-[4-(*N*-Benzyl-*N*-methylaminomethyl)phenyl-amino]ethylidene]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxamide trifluoroacetate



C26 H26 N4 O2 . C2 H F3 O2; Mol wt: 540.5393

ACTION – Antiproliferative agent, an inhibitor of cyclin/cyclin-dependent kinase (CDK) complexes proven to inhibit the proliferation of human leiomyosarcoma SK-UT-1B cells with an IC_{50} value of 0.005 μ M. Other compounds from this series of substituted indolinones include the following:



Compound	R1	R2	R3	X	Formula
284234	Me	H	1-Pip-CH2		C ₂₃ H ₂₆ N ₄ O ₂
284235	Me	H	Br		C ₁₇ H ₁₄ BrN ₃ O ₂
284236	Bu	H	1-Pip-CH2		C ₂₆ H ₃₂ N ₄ O ₂
284237	Me	H	Cl		C ₁₇ H ₁₄ ClN ₃ O ₂

Compound	R1	R2	R3	X	Formula
284238	H	H	H		C ₁₇ H ₁₅ N ₃ O ₂
284239	Me	H	4-Cl-PhCH ₂ NHCH ₂	CF ₃ CO ₂ H	C ₂₅ H ₂₃ ClN ₄ O ₂ .C ₂ HF ₃ O ₂
284240	Me	H	CH ₂ N(Et)CH ₂ Ph	CF ₃ CO ₂ H	C ₂₇ H ₂₈ N ₄ O ₂ .C ₂ HF ₃ O ₂
284241	Me	H	CH ₂ NHCH ₂ Ph		C ₂₅ H ₂₄ N ₄ O ₂
284242	H	H	CH ₂ N(Me)CH ₂ Ph	CF ₃ CO ₂ H	C ₂₅ H ₂₄ N ₄ O ₂ .C ₂ HF ₃ O ₂
284243	Me	H	2,3,4,5-tetrahydro-1H-3-benzazepinyl-CH ₂	CF ₃ CO ₂ H	C ₂₈ H ₂₈ N ₄ O ₂ .C ₂ HF ₃ O ₂
284244	Me	NO ₂	1-Pip-CH ₂		C ₂₃ H ₂₅ N ₅ O ₄
284245	Me	NO ₂	Me		C ₁₈ H ₁₆ N ₄ O ₄

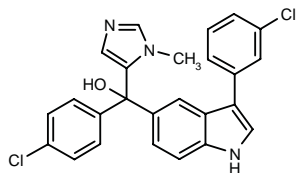
SOURCE – Boehringer Ingelheim.

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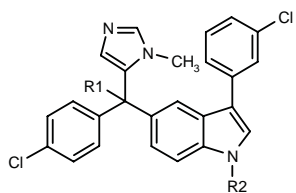
284636

1-(4-Chlorophenyl)-1-[3-(3-chlorophenyl)-1H-indol-5-yl]-1-(1-methyl-1H-imidazol-5-yl)methanol



C₂₅ H₁₉ Cl₂ N₃ O; Mol wt: 448.3511

ACTION – Prenyl transferase inhibitor with potential in the treatment of proliferative disorders such as cancer, restenosis, fibrosis, benign prostatic hyperplasia and atherosclerosis. Other exemplified compounds within this series of imidazolyl derivatives include the following:



Compound	R1	R2	Formula
284638	OH	SO ₂ Me	C ₂₈ H ₂₁ Cl ₂ N ₃ O ₃ S
284639	NH ₂	CON(Me) ₂	C ₂₈ H ₂₅ Cl ₂ N ₃ O
284640	OH	1-pyrrolidinyl-CO	C ₃₀ H ₂₆ Cl ₂ N ₄ O ₂
284641	OH	SO ₂ Ph	C ₃₁ H ₂₃ Cl ₂ N ₃ O ₃ S
284642	OH	4-morpholinyl-SO ₂	C ₂₉ H ₂₆ Cl ₂ N ₄ O ₄ S
284643	NH ₂	Ac	C ₂₇ H ₂₂ Cl ₂ N ₄ O

SOURCE – SCRAS.

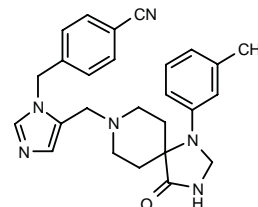
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284653

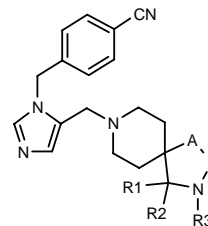
4-[5-[1-(3-Methylphenyl)-4-oxo-1,3,8-triazaspiro[4.5]dec-8-ylmethyl]-1H-imidazol-1-ylmethyl]benzonitrile

4-[5-[1-(3-Methylphenyl)-4-oxospiro[imidazolidine-5,4'-piperidin]-1'-ylmethyl]-1H-imidazol-1-ylmethyl]benzonitrile



C₂₆ H₂₈ N₆ O; Mol wt: 440.5482

ACTION – Agent for the treatment of proliferative disorders such as cancer, restenosis and benign prostatic hyperplasia, an inhibitor of prenyl transferases and the prenylation of the oncogene protein Ras. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	A	B	Formula
284654	H	H	H	N(3-MePh)	-CO-	C ₂₆ H ₂₈ N ₆ O
284655	H	H	H	N(3-MePh)	SO ₂	C ₂₅ H ₂₈ N ₆ O ₂ S
284657	H	H	H	N(4-Cl-3-MePh)	SO ₂	C ₂₅ H ₂₇ ClN ₆ O ₂ S
284658	-O-		3-(CF ₃ O)-PhCH ₂	N(Ph)	-CH ₂ -	C ₃₃ H ₃₁ F ₃ N ₆ O ₂
284659	-O-		2-(CF ₃ O)-PhCH ₂	N(Ph)	-CH ₂ -	C ₃₃ H ₃₁ F ₃ N ₆ O ₂
284660	H	H	3-(CF ₃ O)-PhCH ₂	O	-CO-	C ₂₇ H ₂₆ F ₃ N ₆ O ₃
284661	-O-		3-(CF ₃ O)-PhCH ₂	CH ₂	-CO-	C ₂₈ H ₂₆ F ₃ N ₆ O ₃

SOURCE – Merck & Co.

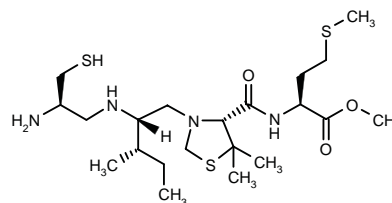
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BIM-46068¹⁻³

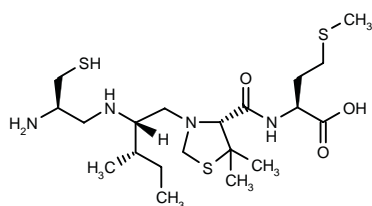
274452

N-[3-[2(S)-[2(R)-Amino-3-sulfanypropylamino]-3(S)-methylpentyl]-5,5-dimethyl-4(R)-thiazolidinylcarbonyl]-L-methionine methyl ester



C₂₁ H₄₂ N₄ O₃ S₃; Mol wt: 494.7858

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase (IC_{50} = 91.4 nM against human enzyme) with high selectivity relative to human geranylgeranyltransferase I (IC_{50} = 268 μ M). Compound showed broad-spectrum cytotoxic activity against wild-type *ras* cell lines including colon HT29, breast MCF-7, glioma U87MG and pancreas HS766 cancer cell lines (IC_{50} = 8.8, 19.4, 26 and 19 μ M, respectively), mutated *Ki-ras* cell lines including pancreas MiaPaCa-2 and CFPAC cell lines (IC_{50} = 8.5 and 22.6 nM, respectively), mutated *N-ras* leukemia HL60 (IC_{50} = 6.6 μ M) and mutated *H-ras* bladder T24 and T24R cell lines (IC_{50} = 10.7 and 37 μ M, respectively). In nude mice implanted with MiaPaCa-2 tumor cells, compound (1-30 mg/kg i.p.) reduced tumor growth in a dose-dependent manner, with a 50% tumor reduction observed 34 days after implantation at the highest dose; no toxic effects were associated with treatment even at the highest dose. Another related compound is:



BIM-46050 [282937]^{1,2}: C₂₀ H₄₀ N₄ O₃ S₃

SOURCE – Biomeasure.

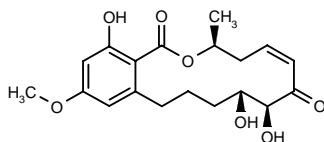
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L-783277¹⁻³

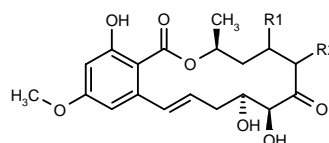
284084

(3*S*,5*Z*,8*S*,9*R*)-8,16-Trihydroxy-3-methyl-14-methoxy-3,4,9,10,11,12-hexahydro-1*H*-2-benzoxacyclotetradecin-1,7(8*H*)-dione

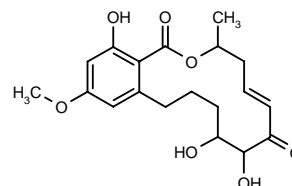


C₁₉ H₂₄ O₇; Mol wt: 364.3916

ACTION – Potent and selective MEK (MAP kinase kinase)/ERK (extracellular regulated kinase) kinase inhibitor isolated from a *Phoma* sp., proven to inhibit MEK activity with an IC_{50} of 4 nM and to have weak inhibitory activity against Lck (IC_{50} = 750 nM) and no activity against Raf kinase, protein kinase C (PKC) or protein kinase A (PKA) activities; it is a time-dependent, ATP-competitive and apparently irreversible inhibitor of MEK. In cell-based assays, compound was found to inhibit Ras-dependent MAP kinase phosphorylation in human tumor PSN-1 cells at submicromolar concentrations, as well as the growth of human epithelial tumor lines with EC_{50} values of 100-200 nM. It is also reported to be effective in inhibiting tumor growth in nude mouse models. Other resorcylic acid lactones are:



Compound	R1	R2	Formula
L-783278 [284086] ^{2,3}	bond		C ₁₉ H ₂₂ O ₇
L-783279 [284087] ^{2,3}	H	H	C ₁₉ H ₂₄ O ₇



L-78329 [284085]¹⁻³: C₁₉ H₂₄ O₇

SOURCE – Merck & Co.

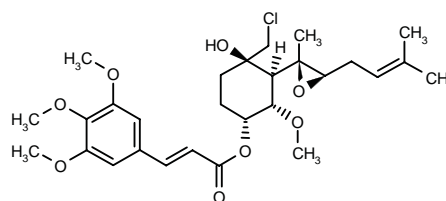
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- Zhao, A. et al. *Resorcylic acid lactones: Naturally occurring potent and selective inhibitors of MEK*. J Antibiot 1999, 52(12): 1086.

ANGIOGENESIS INHIBITORS

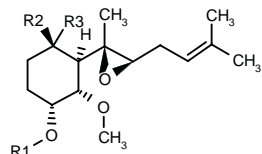
283522

3-(3,4,5-Trimethoxyphenyl)-2(*E*)-propenoic acid (1*R*,2*S*,3*R*,4*R*)-4-(chloromethyl)-4-hydroxy-3-[2(*R*)-methyl-3(*R*)-(3-methyl-2-butenyl)oxiran-2-yl]-2-methoxycyclohexyl ester



C₂₈ H₃₉ Cl O₈; Mol wt: 539.0611

ACTION – Angiogenesis inhibitor, a fumagillol derivative shown to inhibit the proliferation of calf pulmonary artery endothelial (CPAE) cells and murine lymphoma EL-4 cells (IC_{50} = 48 and 11 ng/ml, respectively, vs. 3.2 and 1.6 mg/ml for fumagillin), while being ineffective against murine leukemia P388D1 cells (IC_{50} = 10 g/ml or more). LD_{50} = 2 g/kg p.o. or more in mice. Potentially useful in the treatment of cancer, rheumatoid arthritis, psoriasis or diabetic retinitis. Other compounds from this series of fumagillol derivatives include the following:



Compound	R1	R2	R3	Formula
283525	(E)-4-MeO-PhCH=CHCO	-OCH2-		$C_{26}H_{34}O_6$
283527	(E)-4-Cl-PhCH=CHCO	-OCH2-		$C_{25}H_{31}ClO_5$
283528	(E)-4-NO ₂ -PhCH=CHCO	-OCH2-		$C_{25}H_{31}NO_7$
283531	(E)-4-AcO-PhCH=CHCO	-OCH2-		$C_{27}H_{34}O_7$
283532	(E)-3,5-(MeO)2-4-AcO-PhCH=CHCO	-OCH2-		$C_{29}H_{36}O_9$
283533	(E)-3,4-(MeO)2-4-OH-PhCH=CHCO	-OCH2-		$C_{27}H_{36}O_8$
283534	(E)-4-MeO-PhCH=CHCO	OH	CH ₂ Cl	$C_{26}H_{35}ClO_6$
283535	(E)-4-N(Me)2-PhCH=CHCO	-OCH2-		$C_{27}H_{37}NO_5$
283537	(E)-4-NH ₂ -PhCH=CHCO	-OCH2-		$C_{25}H_{33}NO_5$
283540	(E)-3,4,5-(MeO)3-PhCH=CHCH ₂	-OCH2-		$C_{27}H_{38}O_7$
283541	(E)-4-[N(Me)2CH ₂ CH ₂ O]-PhCH=CHCO	-OCH2-		$C_{28}H_{41}NO_6$
283542	(E)-3-[N(Me)2CH ₂]-4-MeO-PhCH=CHCO	-OCH2-		$C_{29}H_{41}NO_6$
283543	(E)-1,3-benzodioxol-5-yl-CH=CHCO	-OCH2-		$C_{26}H_{32}O_7$
283545	(E)-2-NH ₂ -4,5-(MeO)2-PhCH=CHCO	-OCH2-		$C_{27}H_{37}NO_7$
283547	(E)-4-N(Me)2-PhCH=CHCO	OH	CH ₂ Cl	$C_{27}H_{38}ClNO_5$

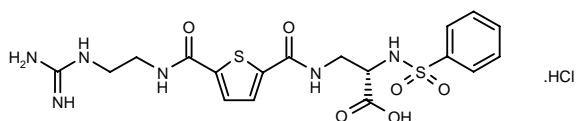
SOURCE – Chong Kun Dang.

REFERENCES

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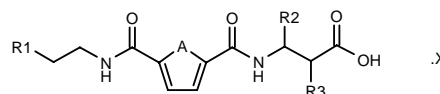
284713

3-[5-[N-(2-Guanidinoethyl)carbamoyl]thien-2-ylcarboxamido]-2(S)-(phenylsulfonamido)propionic acid hydrochloride



C₁₈H₂₂N₆O₆S₂ · HCl; Mol wt: 519.0007

ACTION – An inhibitor of integrins, particularly α_v integrins such as $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins, with potential in the treatment of cancer and tumor metastasis and for inhibiting angiogenesis, as well as for the treatment of osteoporosis, restenosis, ocular diseases, cardiovascular diseases and arthritis. *In vitro*, compound inhibited fibrinogen binding to $\alpha_v\beta_3$ and gpIIb/IIIa with IC_{50} values of 0.00058 and 0.00031 μ M, respectively, and it inhibited osteopontin binding to $\alpha_v\beta_3$ -transfected K562 cells, vitronectin binding to HT29 cells (expressing $\alpha_v\beta_5$) and fibronectin binding to K562 cells (expressing $\alpha_5\beta_1$) with respective IC_{50} values of 0.087, 0.21 and 5.3 μ M. Compound also significantly suppressed vascular endothelial growth factor (VEGF)-stimulated capillary formation in the chick chorioallantoic membrane (CAM) assay by 38% at 33 μ g/mesh and was shown to inhibit the proliferation of HMVEC and HT29 cells with IC_{50} values of 0.87 and 9.9 μ M, respectively. Other compounds from this series of thiophene and furan 2,5-dicarboxamides include the following:



Compound	R1	R2	R3	A	X	Formula
284714	CH ₂ NH ₂	Ph	H	S	CF ₃ CO ₂ H	$C_{18}H_{21}N_5O_4S \cdot C_2HF_3O_2$
284715	CH ₂ NH-C(=NH)NH ₂	Ph	H	S		$C_{19}H_{23}N_5O_4S$
284716	NHC(=NH)NH ₂	H	(S)-NHSO ₂ Ph	O	HCl	$C_{18}H_{22}N_6O_7S \cdot HCl$
284717	NHC(=NH)NH ₂	H	2-pyrimidinyl-NH	S	2CF ₃ CO ₂ H	$C_{16}H_{20}N_6O_4S \cdot 2C_2HF_3O_2$

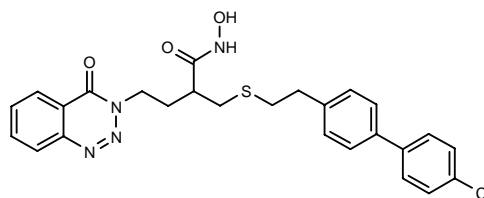
SOURCE – BioChem Pharma.

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- Labrecque, D. et al. (BioChem Pharma Inc.) *Thiophene and furan 2,5-dicarboxamides useful in the treatment of cancer*. WO 0000486.

284924

2-[2-(4'-Chlorobiphenyl-4-yl)ethylsulfanylmethyl]-4-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)butyrylhydroxamic acid



C₂₆H₂₅ClN₄O₃S; Mol wt: 509.0275

ACTION – An inhibitor of matrix metalloproteinases (MMPs) and the production of TNF- α , with potential in the treatment of tumor growth, invasion and metastasis, rheumatoid arthritis, arthrosis, ulcers, atherosclerosis and asthma. Compound inhibited the degradation of collagen induced by IL-1 β in rabbit articular cartilage with an IC_{50} of 1.9 μ M; *in vivo*, it was shown to inhibit the formation of lung metastases in mice bearing B16F10 melanoma by 75% at a dose of 100 mg/kg/day i.p. x 4 days.

SOURCE – ADIR.

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CANSTATIN

283572

Recombinant endogenous 24-kDa fragment of the $\alpha 2$ chain of type IV collagen produced in Escherichia coli and 293 embryonic kidney cells

ACTION – Antineoplastic agent, a fragment of the $\alpha 2$ chain of type IV collagen derived from human basement membrane and subsequently produced by recombinant techniques; it acts by inhibiting angiogenesis and inducing apoptosis. Compound significantly inhibited fetal bovine serum-stimulated endothelial cell proliferation ($ED_{50} = 0.5 \mu\text{g/ml}$), significantly inhibited VEGF (vascular endothelial growth factor)-stimulated human umbilical vein endothelial cell migration (10 ng/ml) and induced apoptosis in endothelial cells by a mechanism associated with down-regulation of the antiapoptotic protein FLIP. Additionally, murine endothelial tube formation in collagen gels was almost completely abolished with 1 μg of compound. Canstatin (10 mg/kg/day i.p.) proved effective in suppressing the growth of small and large human renal cell carcinoma xenografts in athymic nude mice and of established human prostate adenocarcinoma PC-3 in athymic nude or SCID mice; the tumor histology revealed a decrease in CD31-positive vasculature.

SOURCES – Beth Israel Deaconess Medical Center, Boston, MA (US); Ilex Oncology.

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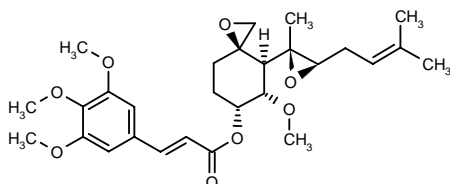
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2. Kamphaus, G.D. et al. *Canstatin: A novel matrix derived inhibitor of angiogenesis and renal cell carcinoma tumor growth*. 32nd Annu Meet Am Soc Nephrol (Nov 5-8, Miami Beach) 1999, Abst A2499.
3. *Ilex Oncology updates investors at healthcare conference*. DailyDrugNews.com (Daily Essentials) 1999, Nov 9.

CKD-731

283526

3-(3,4,5-Trimethoxyphenyl)-2(E)-propenoic acid (3R,4S,5S,6R)-4-[2(R)-methyl-3(R)-(3-methyl-2-butenyl)oxiran-2-yl]-5-methoxy-1-oxaspiro[2.5]oct-6-yl ester

6-O-[3-(3,4,5-Trimethoxyphenyl)-2(E)-propenoyl]-fumagillol



C28 H38 O8; Mol wt: 502.6002

ACTION – Angiogenesis inhibitor, a fumagillin analogue with *in vitro* antiproliferative activity against lymphoma EL-4 cells ($IC_{50} = 0.00015 \text{ ng/ml}$) and calf pulmonary artery endothelial cells ($IC_{50} = 0.00003 \text{ ng/ml}$); compared to the fumagillin analogue TNP-470, compound was 1,000-fold more potent against endothelial cells and 200-fold more potent against lymphoma cells.

SOURCE – Chong Kun Dang.

REFERENCES

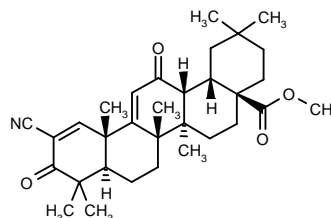
1. Hong, C.I. et al. (Chong Kun Dang Corp.) *Fumagillol derivs. and processes for preparing the same*. WO 9959986.
2. Han, C.K. et al. *Design and synthesis of highly potent fumagillin analogues from homology modeling for a human MetAP-2*. Bioorg Med Chem Lett 2000, 10(1): 39.

OTHER ONCOLYTIC DRUGS

284395¹⁻³

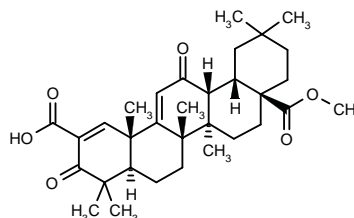
2-Cyano-3,12-dioxoolean-1,9(11)-dien-28-oic acid methyl ester

(6aR,6bS,8aR,12aS,14aR,14bS)-11-Cyano-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydronicene-4a(2H)-carboxylic acid methyl ester



C32 H43 N O4; Mol wt: 505.6947

ACTION – Potent inhibitor of nitric oxide production, as demonstrated in interferon gamma-stimulated mouse macrophages ($IC_{50} = 0.1 \text{ nM}$), with a potency equal to that of dexamethasone ($IC_{50} = 0.1 \text{ nM}$). Potentially useful as an antiinflammatory and chemopreventive agent. Within this series of olean triterpenoids, the following is also specifically claimed:



284394^{1,3} C32 H44 O6

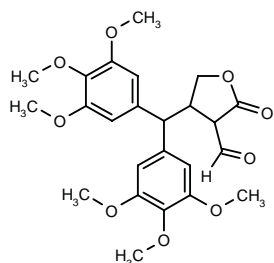
SOURCE – Dartmouth College, Hanover, NH (US).

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1. Gribble, G.W. et al. (Dartmouth College) *Therapeutic compsns. and methods of use*. WO 9965478.
2. Honda, T. et al. *Design and synthesis of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, a novel and highly active inhibitor of nitric oxide production in mouse macrophages*. Bioorg Med Chem Lett 1998, 8(19): 2711.
3. Honda, T. et al. *Novel synthetic oleanate triterpenoids: A series of highly active inhibitors of nitric production in mouse macrophages*. Bioorg Med Chem Lett 1999, 9(24): 3429.

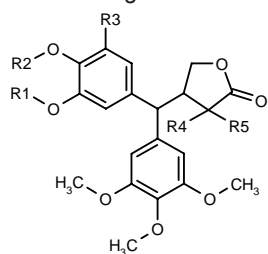
282501

4-[Bis(3,4,5-trimethoxyphenyl)methyl]-2-oxotetrahydrofuran-3-carbaldehyde



C24 H28 O9; Mol wt: 460.4762

ACTION – Antineoplastic agent, a peperomin analogue reported to be devoid of the hypersensitivity towards leukemia cells shown by current anticancer agents such as doxorubicin. Cytotoxicity was evaluated *in vitro* against human colon carcinoma COLO 205, hepatocellular carcinoma HA22T, breast cancer SK-BR-3 and leukemia MOLT-4 cells (IC_{50} = 2.3, 7.1, 4.0 and 2.8 $\mu\text{g/ml}$, respectively, vs. 0.2, 0.2, 0.1 and 0.01 $\mu\text{g/ml}$, respectively, for doxorubicin). Other compounds from this series of α -methylene peperomins and halogenated derivatives thereof include the following:



Compound	R1	R2	R3	R4	R5	Formula
282502	-CH2-		OMe	H	CHO	C ₂₃ H ₂₄ O ₉
282503	-CH2-		H	H	CHO	C ₂₂ H ₂₂ O ₈
282505	Me	Me	OMe	H	CH ₂ OH	C ₂₄ H ₃₀ O ₉
282507	-CH2-		OMe	H	CH ₂ OH	C ₂₃ H ₂₆ O ₉
282510	-CH2-		H	H	CH ₂ OH	C ₂₂ H ₂₄ O ₈
282512	Me	Me	OMe	-CH2-		C ₂₄ H ₂₈ O ₈
282516	-CH2-		OMe	-CH2-		C ₂₃ H ₂₄ O ₈
282518	-CH2-		H	-CH2-		C ₂₂ H ₂₂ O ₇

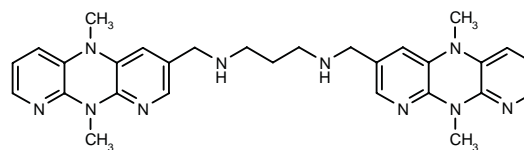
SOURCE – Development Center for Biotechnology, Taipei (TW).

REFERENCES

1. Chou, S.-Y. et al. (Development Center for Biotechnology) *α -Methylene peperomins and halogenated derivs. thereof*. US 5981577.

284142

*N*¹,*N*³-Bis(5,10-dimethyl-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]pyrazin-3-ylmethyl)propane-1,3-diamine



C29 H34 N10; Mol wt: 522.6576

ACTION – Antineoplastic agent whose activity was demonstrated *in vivo* in mice bearing leukemia P388 (T/C x 100 = 150 and 190%, respectively, at 25 and 50 mg/kg i.v. or i.p.) and in mice bearing B16 melanoma (T/C x 100 = 140 and 150%, respectively, at 1.56 and 12.5 mg/kg/day i.p. x 9 days). A representative compound from a series of 5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazine and 5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]pyrazine derivatives.

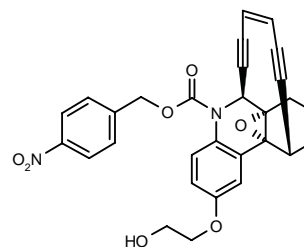
SOURCE – ADIR.

REFERENCES

1. Caubere, P. et al. (ADIR et Cie.) *5,10-Dihydrodipyrido(2,3-*b*:2,3-*e*)pyrazine and 5,10-dihydro(2,3-*b*:3,2-*e*)pyrazine, process for their preparation and pharmaceutical compsns. containing them*. CA 2274733, EP 0963986, FR 2779725, JP 2000007674.

284387

(6*R**,6*aR**,10*R**,10*aS**,14*Z*)-2-(2-Hydroxyethoxy)-7,8,9,10-tetrahydro-6*a*,10*a*-epoxy-6,10-[3]hexene[1,5]dinyphenanthridine-5(6*H*)-carboxylic acid 4-nitrobenzyl ester



C29 H24 N2 O7; Mol wt: 512.5156

ACTION – Antineoplastic agent, an enediyne prodrug activated by a nitroreductase (NTR) enzyme from *Escherichia coli*. The cytotoxicity of compound against a number of cancer cell lines including human ovarian carcinoma SKOV-3, human colon carcinoma WiDr and Chinese hamster lung fibroblast V79 cells increased by 21-135-fold in NTR-expressing cell lines (IC_{50} = 13-24 nM in NTR-expressing lines), indicating its potential as an NTR-mediated gene-directed enzyme prodrug therapy (GDEPT). The efficacy of compound in hypoxic regions of tumor might be limited by its oxygen-dependent cytotoxicity.

SOURCE – University of Auckland, Auckland (NZ).

REFERENCES

1. Denny, W.A. et al. *Enediyne cpds*. WO 9707118.
2. Hay, M.P. et al. *Nitrobenzyl carbamate prodrugs of enediynes for nitroreductase gene-directed enzyme prodrug therapy (GDEPT)*. Bioorg Med Chem Lett 1999, 9(24): 3417.

ACRP30R2

284447

Polypeptide with homology to 30-kDa adipocyte complement-related protein (ACRP30)

ACTION – Polypeptide with homology to 30-kDa adipocyte complement-related protein (ACRP30), a member of the complement C1q/TNF family of proteins known to play a key role in inflammation, cell proliferation, cell death, immunity, obesity, diabetes, and energy metabolism and homeostasis. Polynucleotides encoding said polypeptide, methods for its production, as well as the use thereof in the diagnosis and treatment of the above diseases or as a tool for identifying agonists, antagonists and/or inhibitors thereof for use in therapy, are also disclosed.

SOURCE – SmithKline Beecham.

REFERENCES

1. Hensley, P. et al. (SmithKline Beecham Corp.) *ACRP30R2, a homolog of ACRP30 (30 KD adipocyte complement-related protein)*. WO 9964629.

E6-BP(SD-7)

283179

ACTION – Polypeptide with the ability to specifically bind to human papillomavirus (HPV) E6 protein, a protein linked to cell proliferation regulation, and which may thus be useful for suppressing tumor growth, e.g., in tumor cells misexpressing endogenous E6-BP, as well as for inhibiting papillomavirus infections.

SOURCE – New England Medical Center Hospitals.

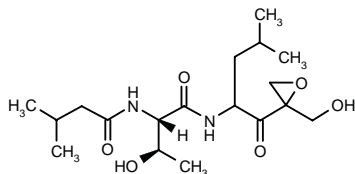
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TMC-96

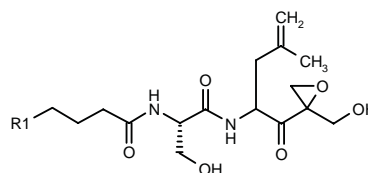
284083

3-Methylbutanoyl-L-threonine *N*-[1-[2-(hydroxymethyl)-oxiran-2-ylcarbonyl]-3-methylbut-3-enyl]amide



C18 H32 N2 O6; Mol wt: 372.4588

ACTION – Proteasome inhibitor extracted from the fermentation broth of *Saccharothrix* sp. TC 1094, proven to inhibit chymotrypsin-like, trypsin-like and peptidyl-glutamyl-peptide hydrolyzing activities of 20S proteasome with IC₅₀ values of 2.9, 36 and 3.5 μM, respectively; it had no effect against m-calpain, cathepsin L or trypsin at concentrations of up to 100 μM. Compound showed strong cytotoxicity against a number of human cancer cell lines including colon carcinoma HCT-116, epitheloid carcinoma HeLa S3, breast adenocarcinoma SK-BR-3, colon adenocarcinoma WiDr and promyelocytic leukemia HL-60 (IC₅₀ = 0.22, 0.21, 0.32, 0.27 and 0.24 μM, respectively), as well as against murine melanoma B16 and murine leukemia P388D1 (IC₅₀ = 0.20 and 0.22 μM, respectively). Also potentially useful for the treatment of inflammatory disorders and muscle wasting associated with pathological conditions such as cancer cachexia, diabetes and sepsis. Other epoxy-β-aminoketones include the following:



Compound	R1	Formula
TMC-86 A [284081]	H	C ₁₆ H ₂₆ N ₂ O ₆
TMC-86 B [284082]	CH ₂ C(Me)2OH	C ₂₀ H ₃₄ N ₂ O ₇

SOURCE – Tanabe Seiyaku.

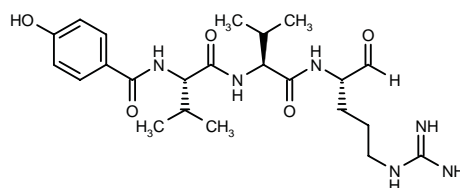
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1. Koguchi, Y. et al. *TMC-86A, B and TMC-96, new proteasome inhibitors from Streptomyces sp. TC 1084 and Saccharothrix sp. TC 1094*. J Antibiot 2000, 53(1): 63.
2. Koguchi, Y. et al. *TMC-86A, B and TMC-96, new proteasome inhibitors from Streptomyces sp. TC 1084 and Saccharothrix sp. TC 1094. I. Taxonomy, fermentation, isolation, and biological activities*. J Antibiot 1999, 52(12): 1069.

TOKARAMIDE A

284385

N-(4-Hydroxybenzoyl)-L-valyl-L-valyl-L-argininal



C23 H36 N6 O5; Mol wt: 476.5744

Pale yellow solid, [α]_D²⁹ –19.0° (c 0.06, MeOH).

ACTION – Cathepsin B inhibitor (IC₅₀ = 29 ng/ml) isolated from the marine sponge *Theonella* aff. *mirabilis*; it is 3- and 4-fold less potent than the known cathepsin inhibitors leupeptin and E-64 (IC₅₀ = 9.2 and 4.9 ng/ml, respectively). Potentially useful for the treatment of cancer, inflammation, trauma and muscular dystrophy.

SOURCES – University of Amsterdam, Amsterdam (NL); University of Tokyo, Tokyo (JP).

REFERENCES

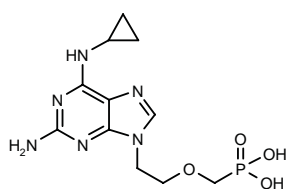
1. Fusetani, N. et al. Tokaramide A, a new cathepsin B inhibitor from the marine sponge *Theonella aff. mirabilis*. Bioorg Med Chem Lett 1999, 9(24): 3397.

cPr-PMEDAP

264562

2-(2,6-Diamino-*N*⁶-cyclopropylpurine-9-yl)ethoxymethylphosphonic acid

*N*⁶-Cyclopropyl-2,6-diamino-9-(2-phosphonomethoxyethyl)purine



C11 H17 N6 O4 P; Mol wt: 328.2673

ACTION – Antineoplastic agent, a derivative of the acyclic nucleoside phosphonate PMEDAP and an intracellular prodrug of 9-(2-phosphonylmethoxyethyl)guanine (PMEG) with cytostatic activity equivalent to that of PMEG against a variety of tumor cell lines including human erythroleukemia K562 cells ($IC_{50} = 1.37 \mu M$) and human lymphoid MOLT4/C8, CEM and Raji cells ($IC_{50} = 0.74, 1.16$ and $1.92 \mu M$, respectively); it is superior to PMEDAP as regards both cytostatic activity and tumor cell differentiation-inducing effects. In a rat choriocarcinoma tumor model, compound at a daily dose of 10 mg/kg i.p. for 10 days induced complete inhibition of tumor development, with prolonged suppression of tumor development after the end of treatment. Compared with the active compound PMEG, the prodrug showed similar antitumor potency *in vivo*, but more prolonged efficacy and reduced renal toxicity.

SOURCES – Gilead; Institute of Organic Chemistry and Biochemistry; Prague (CZ); Rega Institute for Medical Research, Leuven (BE).

REFERENCES

1. Holy, A. and De Clercq, E.D.A. (Institute of Organic Chemistry and Biochemistry; Stichting Rega Vzw) *N6-Substd. nucleotide analogues and their use*. US 5977061, WO 9633200.
2. Andrei, G. et al. Antiproliferative effects of acyclic nucleoside phosphonates on human papillomavirus (HPV)-harboring cell lines compared with HPV-negative cell lines. Oncol Res 1998, 10(10): 523.
3. Compton, M.L. et al. 9-(2-Phosphonylmethoxyethyl)-*N*-6-cyclopropyl-2,6-diaminopurine (Cpr-PMEDAP) as a prodrug of 9-(2-phosphonylmethoxyethyl)guanine (PMEG). Biochem Pharmacol 1999, 58(4): 709.
4. Hatse, S. et al. *N*-6-Cyclopropyl-PMEDAP: A novel derivative of 9-(2-phosphonylmethoxyethyl)-2,6-diaminopurine (PMEDAP) with distinct metabolic, antiproliferative, and differentiation-inducing properties. Biochem Pharmacol 1999, 58(2): 311.
5. Holy, A. et al. Inhibition of murine lymphocyte proliferation by *N*6-substituted acyclic purine nucleoside phosphonates. Coll Czech Chem Commun 1996, 61(Special Issue): S182.
6. Naesens, L. et al. 9-(2-Phosphonylmethoxyethyl)-*N*-6-cyclopropyl-2,6-diaminopurine: A novel prodrug of 9-(2-phosphonylmethoxyethyl)guanine with improved anti-tumor efficacy and selectivity in choriocarcinoma-bearing rats. Oncol Res 1999, 11(4): 195.

hALG-2LP

283727

ACTION – Protein that shows sequence homology with apoptosis-linked gene-2 protein (ALG-2) and which is involved in the modulation of apoptosis. Nucleic acids encoding this protein, as well as antisense nucleic acid molecules, fusion proteins and antibodies, are also disclosed. Potentially useful in the treatment or diagnosis of disorders characterized by deregulated programmed cell death including neurodegenerative and proliferative disorders.

SOURCE – Millennium.

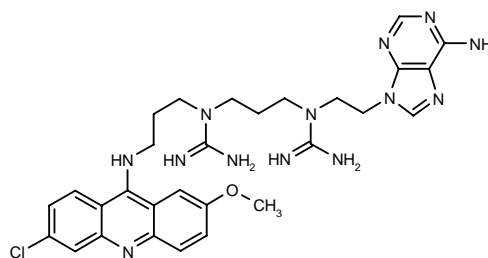
REFERENCES

1. Curtis, R.A.J. (Millennium Pharmaceuticals, Inc.) *ALG-2LP, ALG-2 like molecules and use therefor*. WO 9961459.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

283733

*N*¹-[2-(Adenin-9-yl)ethyl]-*N*^{1'}-[3-(6-chloro-2-methoxyacridin-9-ylamino)propyl]propane-1,3-diguanidine



C29 H36 Cl N13 O; Mol wt: 618.1464

M.p. 225-8 °C.

ACTION – DNA repair inhibitor that strongly and specifically binds to the DNA abasic site without cleaving plasmid abasic DNA; it thereby blocks access to repair enzymes. Compound displayed synergistic *in vitro* cytotoxicity with BCNU against murine leukemia L1210 and human pulmonary adenocarcinoma A549 cells, and it potentiated the *in vivo* effects of BCNU in mice bearing leukemia L1210, increasing 60-day survival from 50% on BCNU 6 mg/kg i.p. to 100% when given at 2.5 mg/kg i.p.

SOURCE – INSERM, Paris Cedex (FR).

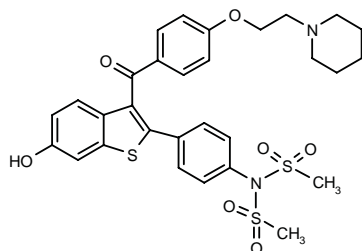
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1. Belmont, P. et al. Abasic site recognition in DNA as a new strategy to potentiate the action of anticancer alkylating drugs? J Med Chem 1999, 42(25): 5153.

LY-329146

250832

N-[4-[6-Hydroxy-3-[4-[2-(4-morpholinyl)ethoxy]benzoyl]-1-benzothien-2-yl]phenyl]-*N*-(methylsulfonyl)methanesulfonamide



C30 H32 N2 O7 S3; Mol wt: 628.7878

ACTION – Potent inhibitor of multidrug resistance-associated protein (MRP1), a raloxifene analogue proven to reverse doxorubicin resistance (by 13.3-fold at 5 μ M) in HL-60/ADR cells expressing MRP1 but not P-glycoprotein (P-gp), and in HL-60/Vinc cells, in which P-gp is highly expressed but MRP1 is not (by 69-fold at 5 μ M). This effect was further assessed in P-gp-expressing CEM/VLB100 cells, in which the compound reversed P-gp-mediated resistance to paclitaxel by 380-fold at the concentration of 5 μ M; no significant effect was observed in the drug-sensitive parental cell line. Compound was also shown to displace [3 H]-vinblastine binding to P-gp in CEM/VLB100 cells (IC_{50} = 20 μ M). In MRP1-expressing HeLa T5 cells, compound at 2.5 μ M completely reversed doxorubicin and vincristine resistance. The observation that compound inhibited the uptake of LTC₄, a known MRP1 substrate, with an IC_{50} of 0.80 μ M, similar to the leukotriene antagonist MK-571 (IC_{50} = 0.50 μ M), indicated that it acts directly on the MRP1 transporter and is consistent with resistance reversal in MRP1-over-expressing cell lines.

SOURCE – Lilly.

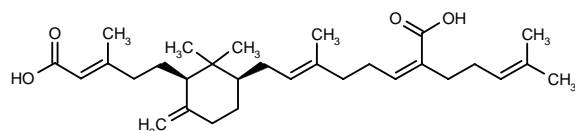
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- Norman, B. et al. *Novel inhibitors of the multidrug resistance-associated protein (MRP)*. Proc Amer Assoc Cancer Res 1997, 38: Abst 2949.
- Norman, B.H. et al. *Reversal of resistance in multidrug resistance protein (MRP1)-overexpressing cells by LY329146*. Bioorg Med Chem Lett 1999, 9: 3381.

MISPYRIC ACID

283380

(+)-8-[(1*R**,3*R**)-3-[4-Carboxy-3-methyl-3(*E*)-butenyl]-2,2-dimethyl-4-methylenecyclohexyl]-6-methyl-2-(4-methyl-3-pentenyl)-2(*Z*),6(*E*)-octadienoic acid



C30 H46 O4; Mol wt: 470.6894

Colorless viscous oil, $[\alpha]_D^{20}$ + 12.5° (c 0.05, MeOH).

ACTION – DNA repair inhibitor, a monocyclic triterpenoid extracted from the dried stem bark of *Mischocarpus pyrifomis*, with inhibitory activity against DNA polymerase β (IC_{50} = 20 and 14 μ M, respectively, in the presence and absence of bovine serum albumin). Compound potentiated the *in vitro* cytotoxicity of bleomycin against mouse lymphoid CCL46 cells (50% reduction of cell viability at the noncytotoxic concentration of 50 μ M together with the nontoxic concentration of bleomycin of 75 nM). Potentially useful for enhancing the efficacy of anticancer treatment.

SOURCE – University of Virginia, Charlottesville, VA (US).

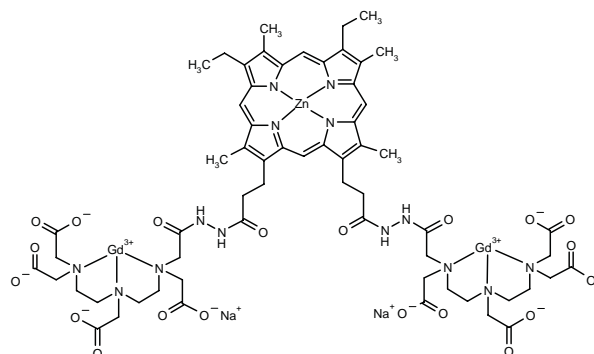
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- Sun, D.-A. et al. *Mispyric acid, a new monocyclic triterpenoid with a novel skeleton from Mischocarpus pyrifomis that inhibits DNA polymerase beta*. J Am Chem Soc 1999, 121(26): 6120.

PHOTOSENSITIZERS

284034

Disodium [μ_3 -[[[7,12-diethyl-3,8,13,17-tetramethyl-21*H*,23*H*-porphine-2,18-dipropanoic acid- κN^{21} , κN^{22} , κN^{23} , κN^{24}] bis[2-[[[2-[[[2-bis[(carboxy- κO)methyl]amino- κN]ethyl][(carboxy- κO)methyl]amino- κN]ethyl][(carboxy- κO)methyl]amino- κN]acetyl- κO]hydrazidato]]-(10-)]zincatedigadolinate(2-)]



C62 H74 Gd2 N14 Na2 O20 Zn; Mol wt: 1761.2150

ACTION – Agent for use in the photodynamic therapy (PDT) of tumors and in magnetic resonance imaging (MRI) diagnostics, reported to possess improved properties compared to structurally related compounds; in particular, it exhibits very good aqueous solubility, good chemical stability, a short half-life and high relaxivity. *In vitro*, compound was shown to be phototoxic to human colon carcinoma HT-29 P9 cells (EC_{50} = 5.1 μ mol/l). A representative compound from a series of 3-,8-substituted deuteroporphyrin derivatives

SOURCE – Schering AG.

REFERENCES

- Platzek, J. et al. (Schering AG) *3-,8-Subst. deuteroporphyrin derivs., pharmaceutical substances containing the same, method for the production and use thereof in photodynamic therapy and MRI diagnosis*. DE 19825512, WO 9962512.

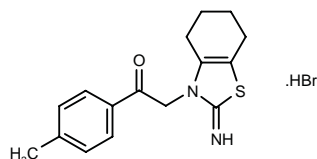
CHEMOPROTECTIVE AGENTS

PIFITHRIN- α

274178

2-(2-Imino-2,3,4,5,6,7-hexahydrobenzothiazol-3-yl)-1-(4-methylphenyl)ethanone hydrobromide

PFT α



C₁₆ H₁₈ N₂ O S . HBr; Mol wt: 367.3091

ACTION – Chemoprotective agent, an inhibitor of *p53* that is able to reversibly block *p53*-dependent transcriptional activation in ConA cells bearing wild-type *p53* gene and apoptosis induced by doxorubicin, paclitaxel, etoposide or cytosine arabinoside in mouse embryo fibroblast C8 cells transformed with *Ela+ras*. *In vivo*, compound was found to protect mice from lethal genotoxic stress associated with anticancer treatment without promoting the formation of tumors. Potentially useful for reducing the side effects of radiation therapy or chemotherapy for human cancers that have lost functional *p53*, and also as a tool to detect clinical situations in which *p53* suppression might be desirable.

SOURCES – University of Illinois, Chicago, IL (US); Quark Biotech.

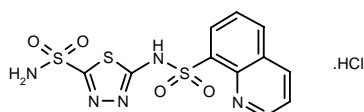
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1. Komarov, P.G. et al. A chemical inhibitor of *p53* that protects mice from the side effects of cancer therapy. *Science* 1999, 285: 1733.

OCULAR MEDICATIONS

283918

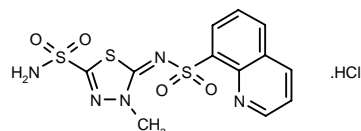
N-[5-(Aminosulfonyl)-1,3,4-thiadiazol-2-yl]quinoline-8-sulfonamide hydrochloride



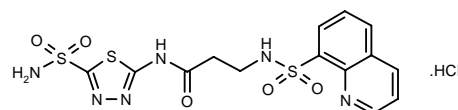
C₁₁ H₉ N₅ O₄ S₃ . HCl; Mol wt: 407.8820

White crystals, *m.p.* > 300 °C.

ACTION – Water-soluble antiglaucoma agent, an inhibitor of carbonic anhydrase (CA) with nanomolar activity against the cytosolic (CA I and CA II) and membrane-bound (CA IV) forms of the enzyme (IC_{50} = 33, 2 and 9 nM, respectively). Compound (50 μ l of a 2% solution instilled in each eye) strongly lowered intraocular pressure (IOP) in both normotensive (–7.2 mmHg at 90 min) and glaucomatous rabbits (–19.9 mmHg at 90 min), with a prolonged duration of action (3-6 h) as compared to dorzolamide. High levels of compound were found in the cornea, aqueous humor and ciliary processes 1 and 2 h after topical administration to normotensive rabbits. Other representative compounds within this series of aromatic/heterocyclic sulfonamides are:



283919: C₁₂ H₁₁ N₅ O₄ S₃ . HCl



283920: C₁₄ H₁₄ N₆ O₅ S₃ . HCl

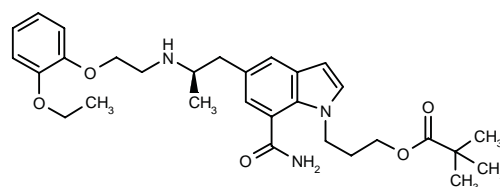
SOURCES – Università degli Studi di Firenze, Firenze (IT); Universidad de Valencia, Valencia (ES).

REFERENCES

1. Borras, J. et al. Carbonic anhydrase inhibitors: Synthesis of water-soluble, topically effective intraocular pressure lowering aromatic/heterocyclic sulfonamides containing 8-quinoline-sulfonyl moieties: Is the tail more important than the ring? *Bioorg Med Chem* 1999, 7(11): 2397.

284281

Pivalic acid 3-[7-carbamoyl-5-[2(*R*)-[2-(2-ethoxyphenoxy)ethylamino]propyl]-1*H*-indol-1-yl]propyl ester



C₃₀ H₄₁ N₃ O₅; Mol wt: 523.6699

ACTION – Agent for the treatment of ocular hypertension, an ester prodrug of a known α_1 -adrenoceptor antagonist reported to possess high membrane permeability and potent and long-lasting intraocular pressure-lowering activity. High conversion to parent compound was observed in aqueous humor of rabbits following ocular administration as eye drops. No mortality was observed following a single administration of 1000 mg/kg p.o. to rats. Another compound from this series of indole derivatives is:

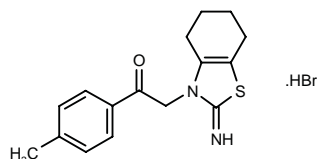
CHEMOPROTECTIVE AGENTS

PIFITHRIN- α

274178

2-(2-Imino-2,3,4,5,6,7-hexahydrobenzothiazol-3-yl)-1-(4-methylphenyl)ethanone hydrobromide

PFT α



C₁₆ H₁₈ N₂ O S . HBr; Mol wt: 367.3091

ACTION – Chemoprotective agent, an inhibitor of *p53* that is able to reversibly block *p53*-dependent transcriptional activation in ConA cells bearing wild-type *p53* gene and apoptosis induced by doxorubicin, paclitaxel, etoposide or cytosine arabinoside in mouse embryo fibroblast C8 cells transformed with *Ela+ras*. *In vivo*, compound was found to protect mice from lethal genotoxic stress associated with anticancer treatment without promoting the formation of tumors. Potentially useful for reducing the side effects of radiation therapy or chemotherapy for human cancers that have lost functional *p53*, and also as a tool to detect clinical situations in which *p53* suppression might be desirable.

SOURCES – University of Illinois, Chicago, IL (US); Quark Biotech.

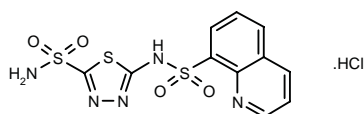
REFERENCES

1. Komarov, P.G. et al. A chemical inhibitor of *p53* that protects mice from the side effects of cancer therapy. *Science* 1999, 285: 1733.

OCULAR MEDICATIONS

283918

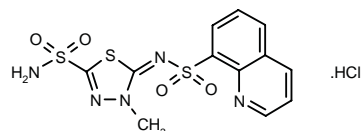
N-[5-(Aminosulfonyl)-1,3,4-thiadiazol-2-yl]quinoline-8-sulfonamide hydrochloride



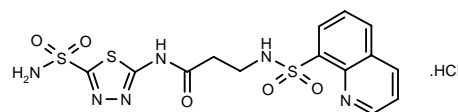
C₁₁ H₉ N₅ O₄ S₃ . HCl; Mol wt: 407.8820

White crystals, *m.p.* > 300 °C.

ACTION – Water-soluble antiglaucoma agent, an inhibitor of carbonic anhydrase (CA) with nanomolar activity against the cytosolic (CA I and CA II) and membrane-bound (CA IV) forms of the enzyme (IC_{50} = 33, 2 and 9 nM, respectively). Compound (50 μ l of a 2% solution instilled in each eye) strongly lowered intraocular pressure (IOP) in both normotensive (–7.2 mmHg at 90 min) and glaucomatous rabbits (–19.9 mmHg at 90 min), with a prolonged duration of action (3-6 h) as compared to dorzolamide. High levels of compound were found in the cornea, aqueous humor and ciliary processes 1 and 2 h after topical administration to normotensive rabbits. Other representative compounds within this series of aromatic/heterocyclic sulfonamides are:



283919: C₁₂ H₁₁ N₅ O₄ S₃ . HCl



283920: C₁₄ H₁₄ N₆ O₅ S₃ . HCl

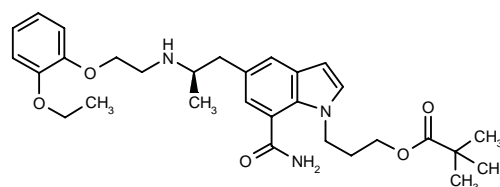
SOURCES – Università degli Studi di Firenze, Firenze (IT); Universidad de Valencia, Valencia (ES).

REFERENCES

1. Borras, J. et al. Carbonic anhydrase inhibitors: Synthesis of water-soluble, topically effective intraocular pressure lowering aromatic/heterocyclic sulfonamides containing 8-quinoline-sulfonyl moieties: Is the tail more important than the ring? *Bioorg Med Chem* 1999, 7(11): 2397.

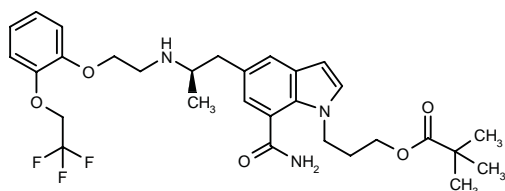
284281

Pivalic acid 3-[7-carbamoyl-5-[2(*R*)-[2-(2-ethoxyphenoxy)ethylamino]propyl]-1*H*-indol-1-yl]propyl ester



C₃₀ H₄₁ N₃ O₅; Mol wt: 523.6699

ACTION – Agent for the treatment of ocular hypertension, an ester prodrug of a known α_1 -adrenoceptor antagonist reported to possess high membrane permeability and potent and long-lasting intraocular pressure-lowering activity. High conversion to parent compound was observed in aqueous humor of rabbits following ocular administration as eye drops. No mortality was observed following a single administration of 1000 mg/kg p.o. to rats. Another compound from this series of indole derivatives is:



284282: C30 H38 F3 N3 O5

SOURCE – Kissei.

REFERENCES

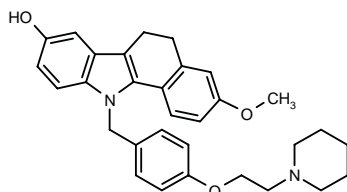
1. Kitazawa, M. et al. (Kissei Pharmaceutical Co., Ltd.) *Indole derivs. and medicinal compns. containing the same*. WO 9943652.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

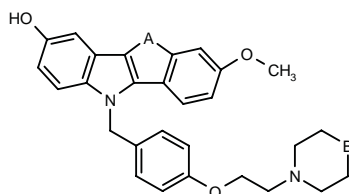
283079

3-Methoxy-11-[4-[2-(1-piperidinyl)ethoxy]benzyl]-6,11-dihydro-5H-benzo[a]carbazol-8-ol



C31 H34 N2 O3; Mol wt: 482.6206

ACTION – Partial estrogen agonist with high binding affinity for the estrogen receptor ($IC_{50} = 0.11 \mu M$ for inhibition of [3H]-17 β -estradiol binding to the human receptor expressed in CHO cells), capable of antagonizing the effects of 17 β -estradiol in a luciferase assay at 1 μM while showing little intrinsic estrogen-agonist activity when dosed alone. Potentially useful in the treatment of osteoporosis, prostatic hypertrophy, male pattern baldness, breast and endometrial cancer, cardiovascular disorders, contraception and for use in hormone replacement therapy in postmenopausal women. Other compounds from this series of benzo-carbazole and indenoindole derivatives include the following:



Compound	A	B	Formula
283081	-CH2-	-CH2-	C ₃₀ H ₃₂ N ₂ O ₃
283082	-(CH2)2-	-(CH2)2-	C ₃₂ H ₃₆ N ₂ O ₃

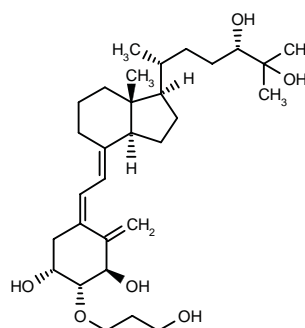
SOURCE – American Home Products.

REFERENCES

1. Miller, C.P. et al. (American Home Products Corp.) *Benzocarbazole and indenoindole derived estrogenic agents*. WO 9958524.

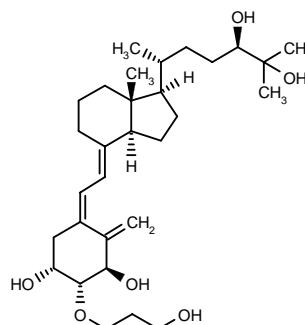
284781

2 β -(3-Hydroxypropoxy)-1 α ,24(S),25-trihydroxyvitamin D₃



C30 H50 O6; Mol wt: 506.7190

ACTION – Vitamin D derivative with affinity for vitamin D receptors (VDR), potentially useful for the treatment of calcium metabolism disorders and cancer. Another compound from this series of 24-hydroxyvitamin D derivatives is:



284785: C30 H50 O6

SOURCE – Chugai.

REFERENCES

1. Hatakeyama, S. et al. (Chugai Pharmaceutical Co. Ltd.) *24-Hydroxyvitamin D derivs*. WO 9943645.

TERIPARATIDE

Rec INN; USAN

253969

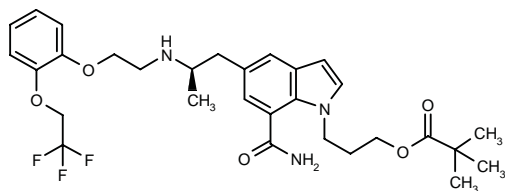
Biosynthetic human parathyroid hormone (hPTH) (1-34)

H-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-OH

rhPTH-(1-34)

LY-333334

C181 H291 N55 O51 S2; Mol wt: 4117.7560



284282: C30 H38 F3 N3 O5

SOURCE – Kissei.

REFERENCES

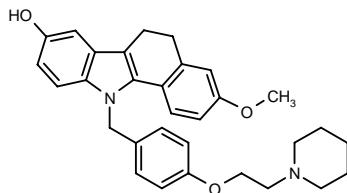
1. Kitazawa, M. et al. (Kissei Pharmaceutical Co., Ltd.) *Indole derivs. and medicinal compns. containing the same*. WO 9943652.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

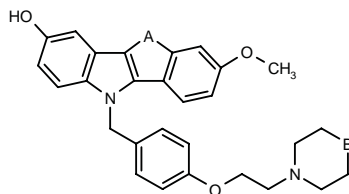
283079

3-Methoxy-11-[4-[2-(1-piperidinyl)ethoxy]benzyl]-6,11-dihydro-5H-benzo[a]carbazol-8-ol



C31 H34 N2 O3; Mol wt: 482.6206

ACTION – Partial estrogen agonist with high binding affinity for the estrogen receptor ($IC_{50} = 0.11 \mu M$ for inhibition of [3H]-17 β -estradiol binding to the human receptor expressed in CHO cells), capable of antagonizing the effects of 17 β -estradiol in a luciferase assay at 1 μM while showing little intrinsic estrogen-agonist activity when dosed alone. Potentially useful in the treatment of osteoporosis, prostatic hypertrophy, male pattern baldness, breast and endometrial cancer, cardiovascular disorders, contraception and for use in hormone replacement therapy in postmenopausal women. Other compounds from this series of benzo-carbazole and indenoindole derivatives include the following:



Compound	A	B	Formula
283081	-CH2-	-CH2-	C ₃₀ H ₃₂ N ₂ O ₃
283082	-(CH2)2-	-(CH2)2-	C ₃₂ H ₃₆ N ₂ O ₃

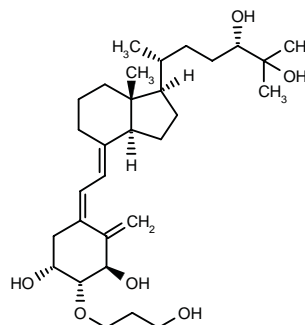
SOURCE – American Home Products.

REFERENCES

1. Miller, C.P. et al. (American Home Products Corp.) *Benzocarbazole and indenoindole derived estrogenic agents*. WO 9958524.

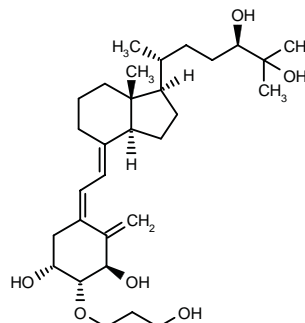
284781

2 β -(3-Hydroxypropoxy)-1 α ,24(S),25-trihydroxyvitamin D₃



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ACTION – Vitamin D derivative with affinity for vitamin D receptors (VDR), potentially useful for the treatment of calcium metabolism disorders and cancer. Another compound from this series of 24-hydroxyvitamin D derivatives is:



284785: C30 H50 O6

SOURCE – Chugai.

REFERENCES

1. Hatakeyama, S. et al. (Chugai Pharmaceutical Co. Ltd.) *24-Hydroxyvitamin D derivs*. WO 9943645.

TERIPARATIDE

Rec INN; USAN

253969

Biosynthetic human parathyroid hormone (hPTH) (1-34)

H-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-OH

rhPTH-(1-34)

LY-333334

C181 H291 N55 O51 S2; Mol wt: 4117.7560

ACTION – Recombinant form of a fragment of human parathyroid hormone* (PTH[1-34]) with high binding affinity for the PTH/PTH-related protein (PTHrP) receptor stably expressed in HEK293 cells ($IC_{50} = 2$ nM), proven to stimulate cAMP production in HEK293 cells transfected with the PTH/PTHrP receptor and in human osteoblast-like Sa OS-2 cells ($IC_{50} = 0.22$ and 0.38 nM, respectively), as well as to stimulate inositol phosphate production. Compound was able to stimulate bone resorption both *in vitro* in neonatal mouse calvarial organ cultures (1.5-1.6-fold increase in mean calcium concentration at 1 nM) and *in vivo* in a rat model of osteoporosis, where doses of 10 and 40 µg/kg/day s.c. for 1-4 weeks induced a dose- and time-dependent increase in trabecular and cortical bone mass. It also increased bone mass and bone strength in ovariectomized cynomolgus monkeys, a model of postmenopausal osteoporosis, without inducing sustained hypercalcemia and hypercalciuria. Currently in phase III trials for the management of osteoporosis in postmenopausal women.

SOURCE – Lilly.

REFERENCES

- Zhang, F. (Eli Lilly and Company) *Crystalline teriparatide*. WO 9931137.
- Black, E.C. et al. *In vivo and in vitro comparison of LY333334, biosynthetic human parathyroid hormone (hPTH) (1-34), with synthetic hPTH(1-34)*. J Bone Miner Res 1997, 12(Suppl. 1): Abst F370.
- Brommage, R. et al. *Daily treatment with human recombinant parathyroid hormone- (1-34), LY333334, for 1 year increases bone mass in ovariectomized monkeys*. J Clin Endocrinol Metab 1999, 84(10): 3757.
- Brommage, R. et al. *Effects of continuation of withdrawal of PTH[1-34] treatment on spine and proximal tibia BMD in ovariectomized monkeys*. J Bone Miner Res 1999, 14(Suppl. 1): Abst F330.
- Brommage, R. et al. *PTH[1-34] increases bone mineral density in ovariectomized monkeys*. 80th Annu Meet Endocr Soc (June 24-27, New Orleans) 1998, Abst P3-78.
- Cole, H.W. et al. *Oral administration of recombinant human PTH (1-34) restores bone mass in osteopenic animals*. J Bone Miner Res 1999, 14(Suppl. 1): Abst 1138.
- Frolik, C.A. et al. *Comparison of biosynthetic human parathyroid hormone (1-34) (LY333334) with a C-terminally substituted analog of human parathyroid hormone-related protein (1-34) (RS-66271): In vitro activity and in vivo pharmacological effects in rats*. 80th Annu Meet Endocr Soc (June 24-27, New Orleans) 1998, Abst P1-590.
- Frolik, C.A. et al. *Comparison of recombinant human PTH(1-34) (LY333334) with a C-terminally substituted analog of human PTH-related protein (1-34) (RS-66271): In vitro activity and in vivo pharmacological effects in rats*. J Bone Miner Res 1999, 14(2): 163.
- Frolik, C.A. et al. *Pharmacokinetic profile of LY333334, biosynthetic human parathyroid hormone (hPTH) (1-34), and serum biochemistry after anabolic or catabolic injection protocols*. J Bone Miner Res 1997, 12(Suppl. 1): Abst F371.
- Galvin, R.J.S. et al. *Human PTH (1-34) administered by once daily dosing is anabolic in mice and increases ex vivo osteoclast differentiation*. J Bone Miner Res 1999, 14(Suppl. 1): Abst SA420.
- Hirano, T. et al. *Anabolic effects of human biosynthetic parathyroid hormone fragment (1-34), LY333334, on remodeling and mechanical properties of cortical bone in rabbits*. J Bone Miner Res 1999, 14(4): 536.
- Hock, J.M. et al. *Synthetic human parathyroid hormone fragment 1-34 (PTH) stimulates both differentiation and apoptosis in trabecular bone cells of young rats, when given once daily to increase bone mass*. 80th Annu Meet Endocr Soc (June 24-27, New Orleans) 1998, Abst P1-610.
- Rowley, E.R. et al. *Low dose effects of PTH on tissue composition in prevention and intervention rat models*. J Bone Miner Res 1999, 14(Suppl. 1): Abst SA434.
- Smith, S.J. et al. *Three-dimensional modeling of the effects of PTH on bone distribution in lumbar vertebra from cynomolgus macaques*. J Bone Miner Res 1999, 14(Suppl. 1): Abst SA433.
- Stanislaus, D. et al. *Regulation of caspase activity in trabecular bone of young rats treated once daily with human parathyroid hormone, rhPTH 1-34 (LY333334) for up to 6 days*. J Bone Miner Res 1999, 14(Suppl. 1): Abst F383.

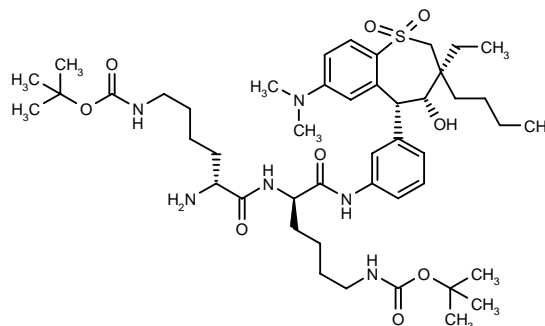
16. Turner, C.H. et al. *In primates, treatment with PTH (1-34), LY333334, increases bone strength at trabecular bone sites without compromising the strength of cortical bone*. J Bone Miner Res 1999, 14(Suppl. 1): Abst SA421.

*See also **Teriparatide acetate** Drug Data Rep 1987, 09(01): 88, a synthetic form developed for use as a diagnostic by Rhône-Poulenc Rorer (Aventis Pharma).

TREATMENT OF LIPOPROTEIN DISORDERS

284328

N^2 -[N^6 -(*tert*-Butoxycarbonyl)-D-lysyl]- N^6 -(*tert*-butoxycarbonyl)- N^1 -[3-[3(*S**)-butyl-7-(dimethylamino)-3-ethyl-4(*R**)-hydroxy-1,1-dioxo-2,3,4,5-tetrahydrobenzo-thiepin-5(*R**)-yl]phenyl]-D-lysylamide



C46 H74 N6 O9 S; Mol wt: 887.1896

ACTION – Hypolipidemic agent, a representative compound from a series of benzo[b]thiepine-1,1-dioxide derivatives proven to reduce fecal excretion of [14 C]-taurocholic acid in rats with an ED_{200} value of 0.04 mg/kg/day p.o.

SOURCE – Aventis Pharma.

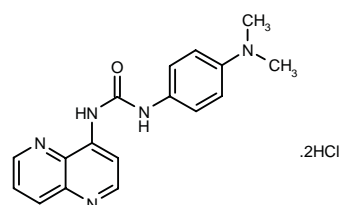
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- Frick, W. et al. (Hoechst Marion Roussel Deutschland GmbH) *Benzo[b]thiepine-1,1-dioxide derivs., a method for the production thereof, medicaments containing these cpds., and their use*. DE 19825804, WO 9964410.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

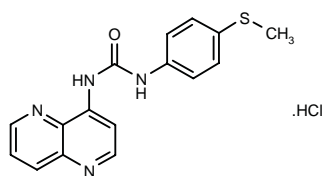
283077

N -[4-(Dimethylamino)phenyl]- N' -(1,5-naphthyridin-4-yl)urea dihydrochloride



C17 H17 N5 O . 2HCl; Mol wt: 380.2771

ACTION – Agent for the treatment of obesity and sleep disorders, a human orexin-1 (HFGAN72) receptor antagonist ($pK_b > 7$ in HEK293 cells expressing the human orexin-1 receptor). Another compound from this series of phenylurea and phenylthiourea derivatives is:



283078: C₁₆ H₁₄ N₄ O S . HCl

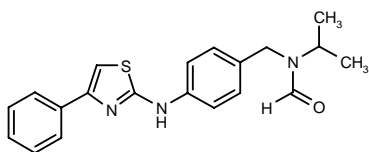
SOURCE – SmithKline Beecham.

REFERENCES

1. Johns, A. and Porter, R.A. (SmithKline Beecham plc) *Phenylurea and phenylthiourea derivs.* WO 9958533.

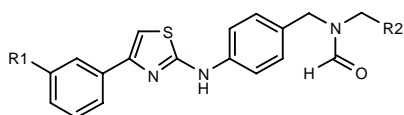
284346

N-Isopropyl-*N*-[4-(4-phenylthiazol-2-ylamino)benzyl]-formamide



C₂₀ H₂₁ N₃ O S; Mol wt: 351.4719

ACTION – Antiobesity agent, a selective neuropeptide Y (NPY) receptor subtype Y₅ antagonist reported to inhibit food intake in food-deprived or NPY-treated rats and spontaneous feeding in obese Zucker rats and *ob/ob* mice after oral, i.p., s.c., i.v. or transdermal administration. Other specifically claimed compounds from this series of aminoazole derivatives include the following:



Compound	R1	R2	Formula
284347	H	2-THF	C ₂₂ H ₂₃ N ₃ O ₂ S
284348	F	cyclopropyl	C ₂₁ H ₂₀ FN ₃ OS

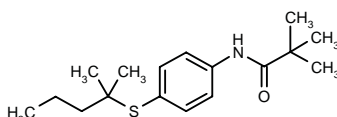
SOURCE – Novartis.

REFERENCES

1. Bühlmayr, P. (Novartis AG) *Aminoazole cpds.* DE 19824175, WO 9962892.

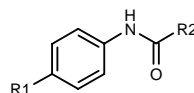
284471

N-[4-(1,1-Dimethylbutylsulfanyl)phenyl]pivalamide



C₁₇ H₂₇ N O S; Mol wt: 293.4723

ACTION – Selective neuropeptide Y (NPY) Y₅ receptor antagonist, potentially useful for the treatment of eating disorders and diabetes. Other exemplified compounds include the following:



Compound	R1	R2	Formula
284472	t-BuCH ₂ S	t-Bu	C ₁₆ H ₂₅ NOS
284473	cyclopentyl-CH ₂ C(Me) ₂ S	t-Bu	C ₂₀ H ₃₁ NOS
284474	COCH ₂ C(Me) ₂ Et	4-Pyr-CH ₂ CH ₂ N(Me)	C ₂₂ H ₂₉ N ₃ O ₂
284475	COC(Me) ₂ Pr	4-(cyclopropyl-CH ₂ NH)-cyclohexyl-N(Me)	C ₂₅ H ₃₉ N ₃ O ₂
284476	CH ₂ C(Me) ₂ Pr	cis-4-(cyclopropyl-CH ₂ NH)-cyclohexyl-N(Me)	C ₂₅ H ₄₁ N ₃ O

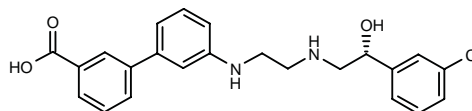
SOURCE – Schering-Plough.

REFERENCES

1. Dugar, S. et al. (Schering Corp.) *Neuropeptide Y5 receptor antagonists.* WO 9964394.

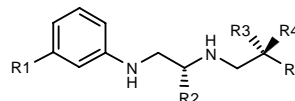
284782

3'-[2-[2-(*R*)-(3-Chlorophenyl)-2-hydroxyethylamino]ethyl-amino]biphenyl-3-carboxylic acid



C₂₃ H₂₃ Cl N₂ O₃; Mol wt: 410.8987

ACTION – Agent for the treatment of obesity, hyperglycemia, diabetes and hyperlipidemia, a potent human β₃-adrenoceptor agonist (EC₅₀ = 1 nM or less for stimulation of cAMP in CHO cells transfected with the human receptor) with > 300-fold selectivity over β₁- and β₂-adrenoceptors. Within this series of biaryl derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
284783	2-Me-5-CO ₂ H-Ph	H	OH	H	3-Cl-Ph	C ₂₄ H ₂₅ ClN ₂ O ₃
284784	3-CO ₂ H-Ph	H	H	OH	CH ₂ O-Ph	C ₂₄ H ₂₆ N ₂ O ₄
284786	2,4-(CO ₂ H) ₂ -Ph	Me	OH	H	3-Cl-Ph	C ₂₅ H ₂₅ ClN ₂ O ₅
284787	5-CO ₂ H-3-Pyr	H	OH	H	3-Cl-Ph	C ₂₂ H ₂₂ ClN ₃ O ₃

SOURCE – Glaxo Wellcome.

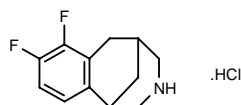
REFERENCES

1. Donaldson, K.H. et al. (Glaxo Group Ltd.) *Therapeutic biaryl derivs.* WO 9965877.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

282726

7,8-Difluoro-1,5-methano-1,2,3,4,5,6-hexahydro-3-benzazocine hydrochloride



C₁₂ H₁₃ F₂ N . HCl; Mol wt: 245.6986

ACTION – Agent that binds to neuronal nicotinic acetylcholine receptor sites, with potential in the treatment of nicotine addiction or for aiding in smoking cessation, as well as for a wide range of other disorders such as inflammatory bowel disease, irritable bowel syndrome, pain, anxiety, depression, sleep disorders, cognitive dysfunction, obesity, cardiac arrhythmias, stroke, Parkinson's disease and senile dementia. A representative compound from a series of aryl fused azapolycyclic derivatives.

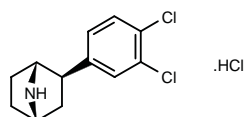
SOURCE – Pfizer.

REFERENCES

1. Coe, J.W. (Pfizer Products Inc.) *Aryl fused azapolycyclic cpds.* WO 9955680.

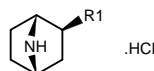
282792

exo-2-(3,4-Difluorophenyl)-7-azabicyclo[2.2.1]heptane hydrochloride



C₁₂ H₁₃ F₂ N . HCl; Mol wt: 245.6986

ACTION – Agent that binds to neuronal nicotinic acetylcholine receptor sites with potential in the treatment of nicotine addiction or for aiding in smoking cessation, as well as for a wide range of other disorders such as inflammatory bowel disease, irritable bowel syndrome, pain, anxiety, depression, sleep disorders, cognitive dysfunction, obesity, cardiac arrhythmias, stroke, Parkinson's disease and senile dementia. A representative compound from a series of 7-aza-bicyclo[2.2.1]heptane derivatives, wherein the following are also included:



Compound	R1	Formula
282793	4-Cl-3-F-Ph	C ₁₂ H ₁₃ ClFN.HCl
282796	3-F-4-Me-Ph	C ₁₃ H ₁₆ FN.HCl
282797	4-CN-Ph	C ₁₃ H ₁₄ N ₂ .HCl
282798	4-(MeSO ₂)-Ph	C ₁₃ H ₁₇ NO ₂ S.HCl
282799	6-MeO-2-Pyr	C ₁₂ H ₁₆ N ₂ O.HCl
282800	6-quinoxaliny	C ₁₄ H ₁₅ N ₃ .HCl

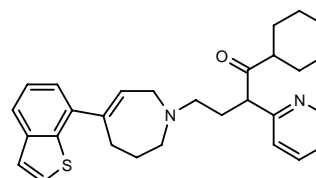
SOURCE – Pfizer.

REFERENCES

1. Yohannes, D. and Bundesmann, M.W. (Pfizer Products Inc.) *7-Aza-bicyclo[2.2.1]-heptane derivs., their preparation and use according o their affinity for neuronal nicotinic acetylcholine receptors.* CA 2269994, EP 0955301, JP 1999322751.

284930

4-[5-(1-Benzothiophen-7-yl)-2,3,4,7-tetrahydro-1H-azepin-1-yl]-1-cyclohexyl-2-(2-pyridinyl)-1-butanone



C₂₉ H₃₄ N₂ O S; Mol wt: 458.6666

ACTION – Combined 5-HT_{1A} and 5-HT_{2A} receptor antagonist and 5-HT reuptake inhibitor with potential for alleviating the symptoms of tobacco or nicotine withdrawal and for the treatment of anxiety, depression, hypertension, cognitive disorders, psychosis, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, eating disorders, obesity, substance abuse, obsessive-compulsive disorder, panic disorder and migraine. A representative compound from a series of azepine derivatives.

SOURCE – Lilly.

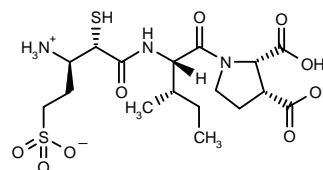
REFERENCES

1. Hauser, K.L. et al. (Eli Lilly and Company) *Azepine derivs. having effects on serotonin related systems.* WO 0000203.

PHARMACOLOGICAL TOOLS

283735

1-[[3(R)-Amino-2(S)-sulfanyl-3-(2-sulfoethyl)propionyl]-L-isoleucyl]pyrrolidine-2(S),3(R)-dicarboxylic acid inner salt



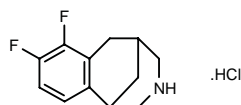
C₁₇ H₂₉ N₃ O₉ S₂; Mol wt: 483.5601

White solid.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

282726

7,8-Difluoro-1,5-methano-1,2,3,4,5,6-hexahydro-3-benzazocine hydrochloride



C₁₂ H₁₃ F₂ N . HCl; Mol wt: 245.6986

ACTION – Agent that binds to neuronal nicotinic acetylcholine receptor sites, with potential in the treatment of nicotine addiction or for aiding in smoking cessation, as well as for a wide range of other disorders such as inflammatory bowel disease, irritable bowel syndrome, pain, anxiety, depression, sleep disorders, cognitive dysfunction, obesity, cardiac arrhythmias, stroke, Parkinson's disease and senile dementia. A representative compound from a series of aryl fused azapolycyclic derivatives.

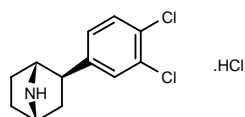
SOURCE – Pfizer.

REFERENCES

1. Coe, J.W. (Pfizer Products Inc.) *Aryl fused azapolycyclic cpds.* WO 9955680.

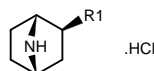
282792

exo-2-(3,4-Difluorophenyl)-7-azabicyclo[2.2.1]heptane hydrochloride



C₁₂ H₁₃ F₂ N . HCl; Mol wt: 245.6986

ACTION – Agent that binds to neuronal nicotinic acetylcholine receptor sites with potential in the treatment of nicotine addiction or for aiding in smoking cessation, as well as for a wide range of other disorders such as inflammatory bowel disease, irritable bowel syndrome, pain, anxiety, depression, sleep disorders, cognitive dysfunction, obesity, cardiac arrhythmias, stroke, Parkinson's disease and senile dementia. A representative compound from a series of 7-aza-bicyclo[2.2.1]heptane derivatives, wherein the following are also included:



Compound	R1	Formula
282793	4-Cl-3-F-Ph	C ₁₂ H ₁₃ ClFN.HCl
282796	3-F-4-Me-Ph	C ₁₃ H ₁₆ FN.HCl
282797	4-CN-Ph	C ₁₃ H ₁₄ N ₂ .HCl
282798	4-(MeSO ₂)-Ph	C ₁₃ H ₁₇ NO ₂ S.HCl
282799	6-MeO-2-Pyr	C ₁₂ H ₁₆ N ₂ O.HCl
282800	6-quinoxaliny	C ₁₄ H ₁₅ N ₃ .HCl

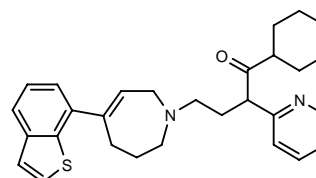
SOURCE – Pfizer.

REFERENCES

1. Yohannes, D. and Bundesmann, M.W. (Pfizer Products Inc.) *7-Aza-bicyclo[2.2.1]-heptane derivs., their preparation and use according o their affinity for neuronal nicotinic acetylcholine receptors.* CA 2269994, EP 0955301, JP 1999322751.

284930

4-[5-(1-Benzothiophen-7-yl)-2,3,4,7-tetrahydro-1H-azepin-1-yl]-1-cyclohexyl-2-(2-pyridinyl)-1-butanone



C₂₉ H₃₄ N₂ O S; Mol wt: 458.6666

ACTION – Combined 5-HT_{1A} and 5-HT_{2A} receptor antagonist and 5-HT reuptake inhibitor with potential for alleviating the symptoms of tobacco or nicotine withdrawal and for the treatment of anxiety, depression, hypertension, cognitive disorders, psychosis, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, eating disorders, obesity, substance abuse, obsessive-compulsive disorder, panic disorder and migraine. A representative compound from a series of azepine derivatives.

SOURCE – Lilly.

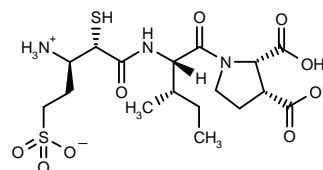
REFERENCES

1. Hauser, K.L. et al. (Eli Lilly and Company) *Azepine derivs. having effects on serotonin related systems.* WO 0000203.

PHARMACOLOGICAL TOOLS

283735

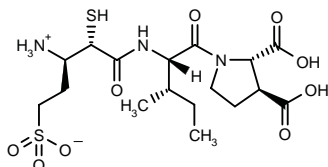
1-[[3(R)-Amino-2(S)-sulfanyl-3-(2-sulfoethyl)propionyl]-L-isoleucyl]pyrrolidine-2(S),3(R)-dicarboxylic acid inner salt



C₁₇ H₂₉ N₃ O₉ S₂; Mol wt: 483.5601

White solid.

ACTION – Potent aminopeptidase A (APA) inhibitor ($K_i = 0.873$ nM) with high selectivity over other zinc metalloproteinases such as aminopeptidase N (APN), angiotensin-converting enzyme and neutral endopeptidase ($K_i = 16,400$, 259 and 219 nM, respectively). Compound was more potent and selective than the reference APA inhibitor amastatin ($K_i = 250$ and 19 nM against APA and APN, respectively). Another related compound is:



283736: C17 H29 N3 O9 S2

SOURCE – INSERM, Paris Cedex (FR).

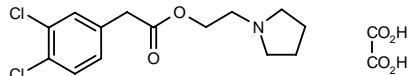
REFERENCES

1. Davis, C. et al. *Investigation of subsite preferences in aminopeptidase A (EC 3.4.11.7) led to the design of the first highly potent and selective inhibitors of this enzyme.* J Med Chem 1999, 42(25): 5197.

AC-915

284566

2-(3,4-Dichlorophenyl)acetic acid 2-(1-pyrrolidiny)ethyl ester oxalate



C14 H17 Cl2 N O2 . C2 H2 O4; Mol wt: 392.2331

ACTION – High-affinity σ_1 -receptor ligand ($K_i = 4.89$ nM for displacement of [3 H]-(+)-pentazocine binding) with high selectivity over σ_2 -receptors ($K_i > 10$ μ M). Potentially useful as a masking agent in σ_2 receptor binding assays.

SOURCES – University of Maryland, Baltimore, MD (US); National Institutes of Health, Bethesda, MD (US).

REFERENCES

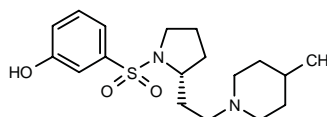
1. Maeda, D.Y. et al. *A σ_1 receptor selective analogue of BD1008. A potential substitute for (+)-opioids in σ receptor binding assays.* Bioorg Med Chem Lett 2000, 10(1): 17.

SB-269970

284712

3-[2-(R)-[2-(4-Methylpiperidin-1-yl)ethyl]pyrrolidin-1-ylsulfonfyl]phenol

SB-269970-A



C18 H28 N2 O3 S; Mol wt: 352.4962

ACTION – Potent and selective 5-HT₇ receptor antagonist ($pK_i = 8.9$ for human receptors) with at least 100-fold selectivity over other 5-HT receptor subtypes, except human 5-HT_{5a} receptors ($pK_i = 7.2$). In *in vitro* functional assays, compound exhibited competitive antagonism against 5-CT-stimulated adenylyl cyclase activity in HEK293 cells expressing human cloned 5-HT₇ receptors and in guinea pig hippocampal membranes ($pA_2 = 8.52$ and $pK_B = 8.3$, respectively). The tritiated compound was shown to bind saturably, monophasically and reversibly to human cloned 5-HT₇ receptors expressed in HEK293 cells, giving a K_d of 1.3 nM, and appeared to label the same receptor population as the known 5-HT₇ receptor agonist [3 H]-5-CT. Potentially useful as a pharmacological tool for studying the role of this receptor in native tissue function.

SOURCE – SmithKline Beecham.

REFERENCES

1. Forbes, I.T. et al. (SmithKline Beecham plc) *Sulphonamide derivs. and their use in the treatment of CNS disorders.* WO 9748681.

2. Lovell, P.J. et al. *A novel, potent, and selective 5-HT₇ antagonist: (R)-3-(2-(4-Methylpiperidin-1-yl)ethyl)pyrrolidine-1-sulfonylphenol (SB-269970).* J Med Chem 2000, 43(3): 342.

3. Price, G.W. et al. *[3 H]-SB-269970: A selective antagonist radioligand for 5-HT₇ receptors.* Br J Pharmacol 1999, 128(Suppl.): Abst 233P.

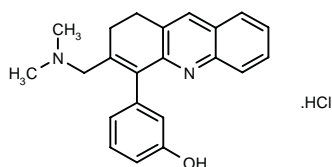
4. Thomas, D.R. et al. *SB-269970 is a potent and selective antagonist at human cloned and guinea-pig brain 5-HT₇ receptors.* Br J Pharmacol 1999, 128(Suppl.): Abst 232P.

ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

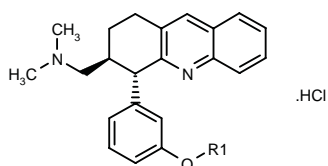
284887

3-[2-(Dimethylaminomethyl)-3,4-dihydroacridin-1-yl]-phenol hydrochloride

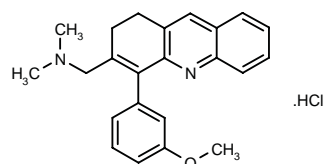


C₂₂ H₂₂ N₂ O . HCl; Mol wt: 366.8897

ACTION – Analgesic agent with high affinity for δ -opioid receptors ($K_i = 3.84 \pm 1.59$ nM in rat brain membrane homogenates). Other compounds within this series of acridine derivatives include the following:



Compound	R1	Formula
284890	Me	C ₂₃ H ₂₆ N ₂ O.HCl
284892	H	C ₂₂ H ₂₄ N ₂ O.HCl



284888: C₂₃ H₂₄ N₂ O . HCl

SOURCE – Grünenthal.

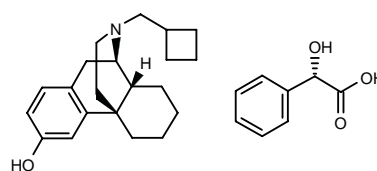
REFERENCES

1. Pütz, C.K. et al. (Grünenthal GmbH) *Acridine derivs.* CA 2276764, EP 0970949, JP 2000026426.

MCL-101

283708

(-)-N-(Cyclobutylmethyl)morphinan-3-ol (S)-mandelate



C₂₁ H₂₉ N O . C₈ H₈ O₃; Mol wt: 463.6143

M.p. 201-2 °C.

ACTION – Mixed κ - and μ -receptor agonist with high affinity for both receptors ($K_i = 0.073$ and 0.12 nM, respectively) and 18-fold selectivity over δ -receptors ($K_i = 1.3$ nM). *In vivo*, compound showed full agonist activity at κ - and μ -receptors, as demonstrated in the tail-flick and acetic acid-induced writhing tests in mice ($ED_{50} = 7.3$ and 0.79 nmol i.c.v., respectively), and was a weak μ -receptor antagonist, partially antagonizing morphine-induced analgesia at a dose that did not produce antinociception by itself. Potentially useful as an opioid analgesic, as well as for the treatment of cocaine dependency.

SOURCES – Harvard Medical School, Boston, MA (US); RBI; University of Rochester Medical Center, Rochester, NY (US).

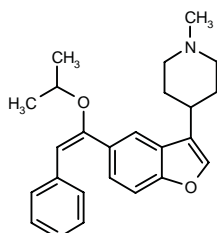
REFERENCES

1. Gates, M.D. Jr. *N-Cyclopropylmethyl- and -cyclobutylmethyl-morphinans.* US 3285922.
2. Monkovic, I. and Wong, H. (Bristol-Myers Squibb Co.) *New synthesis for the preparation of 3-hydroxy-N-alkylisomorphinans.* US 3910919.
3. Monkovic, I. and Wong, H. (Bristol-Myers Squibb Co.) *Synthesis for the preparation of 3-hydroxy-N-alkylisomorphinans.* US 3803150.
4. Monkovic, I. and Wong, H. *Synthetic morphinans and hasubanans. VI. Total synthesis of 3-hydroxyisomorphinans, 3-hydroxyhasubanans, and 3,9-dihydroxyhasubanans.* Can J Chem 1976, 54(6): 883.
5. Neumeyer, J.L. et al. *Synthesis and opioid receptor affinity of morphinan and benzomorphan derivatives: Mixed κ agonists and mu agonists/antagonists as potential pharmacotherapeutics for cocaine dependence.* J Med Chem 2000, 43(1): 114.

ANTIMIGRAINE DRUGS

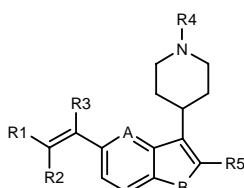
285031

4-[5-(1-Isopropoxy-2-phenylvinyl)-1-methyl-1-benzofuran-3-yl]piperidine

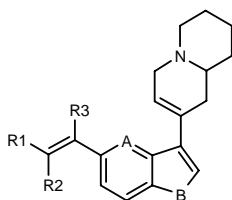


C₂₅ H₂₉ N O₂; Mol wt: 375.5091

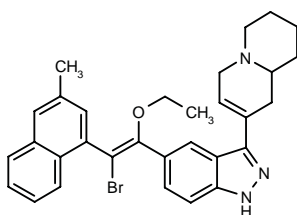
ACTION – Agent for the treatment of migraine and associated disorders, a 5-HT_{1F} receptor agonist that inhibits neuronal peptide extravasation due to stimulation of the trigeminal ganglia. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	A	B	Formula
285032	Et	4-MeO- -1-Naph	OMe	i-Pr	Bu	CH	S	C ₃₆ H ₄₅ NO ₂ S
285033	3-pyrrolyl	C5H11	H	cyclopropyl	Bu	N	NH	C ₃₀ H ₄₂ N ₄
285036	2-N(Me)2- -1-Naph	Pr	i-Pr	CH(Me)Et	t-Bu	CH	O	C ₄₁ H ₅₆ N ₂ O



Compound	R1	R2	R3	A	B	Formula
285038	C6H13	3-F-4-MeO-Ph	I	CH	O	C ₃₂ H ₃₇ FINO ₂
285039	3-CF3O- -1-Naph	CH(Me)Et	Et	N	NH	C ₃₅ H ₃₈ F ₃ N ₃ O



285034: C₃₁ H₃₂ Br N₃ O

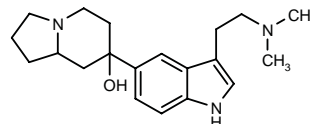
SOURCE – Lilly.

REFERENCES

1. Krushinski, J.H. Jr. et al. (Eli Lilly and Company) 5-HT_{1F} agonists. WO 0000490.

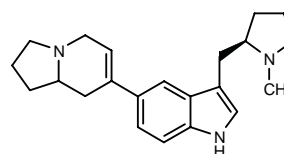
285480

7-[3-[2-(Dimethylamino)ethyl]-1 H-indol-5-yl]perhydro-indolizin-7-ol



C₂₀ H₂₉ N₃ O; Mol wt: 327.4691

ACTION – Antimigraine agent, a selective 5-HT_{1D} receptor agonist (> 90% inhibition of [³H]-HT binding at 100 nM). Another compound from this series of 5-bicycloindole derivatives is:



285481: C₂₂ H₂₉ N₃

SOURCE – NPS Allelix.

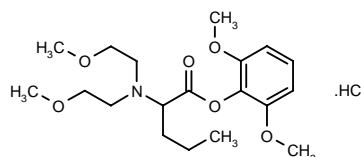
REFERENCES

1. Slassi, A. et al. (NPS Allelix Corp.) 5-Bicycloindole cpds. WO 0004019.

ANESTHETIC DRUGS

285771

2-[N,N-Bis(2-methoxyethyl)amino]pentanoic acid 2,6-dimethoxyphenyl ester hydrochloride



C₁₉ H₃₁ N O₆ . HCl; Mol wt: 405.9158

ACTION – Water-soluble general anesthetic for intravenous administration that acts by allosterically modulating GABA_A receptors, as demonstrated by inhibition of [³⁵S]-TBPS binding to rat whole brain membranes (IC₅₀ = 4.2 μM). Hypnotic activity was demonstrated *in vivo* in mice by a hypnotic dose (HD₅₀; dose causing loss of righting reflex in 50% of the animals for a period of no less than 30 s after i.v. administration over 10 s) of 12 μmol/kg. In addition, compound may also be used in the treatment of GABA-related diseases such as anxiety, stress, sleep disorders, postnatal depression and premenstrual syndrome. A representative compound from a series of α-amino acid phenyl ester derivatives.

SOURCE – Akzo Nobel.

REFERENCES

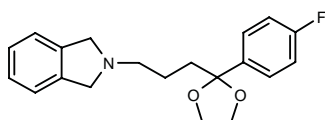
1. Hamilton, N.M. (Akzo Nobel N.V.) *α-Amino acid phenyl ester derivs.* WO 0005196.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

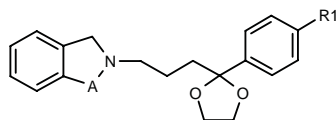
285055

2-[3-[2-(4-Fluorophenyl)-1,3-dioxolan-2-yl]propyl]-2,3-dihydro-1*H*-isoindole



C20 H22 F N O2; Mol wt: 327.3968

ACTION – Agent for the treatment of CNS disorders such as sleep disorders, anxiety, depression and schizophrenia, a 5-HT₇ receptor antagonist. Other bicyclic compounds include the following:



Compound	R1	A	Formula
285056	Br	-CH2-	C ₂₀ H ₂₂ BrNO ₂
285057	Me	-CH2-	C ₂₁ H ₂₅ NO ₂
285058	F	-(CH2)2-	C ₂₁ H ₂₄ FNO ₂

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Cain, G.A. and McElroy, J.F. (DuPont Pharmaceuticals Co.) *5-HT₇ receptor antagonists.* WO 0000472.

DEXMEDETOMIDINE* HYDROCHLORIDE

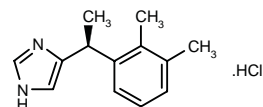
Rec INN; BANM; USAN

145584

(+)-4-[(*S*)-α,2,3-Trimethylbenzyl]imidazole monohydrochloride

(+)-(*S*)-4-[1-(2,3-Dimethylphenyl)ethyl]-1*H*-imidazole monohydrochloride

MPV-1440



C13 H16 N2 . HCl; Mol wt: 236.7443

ACTION – Relatively selective α₂-adrenoceptor agonist with sedative properties.

INDICATION – Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting (treatment not to exceed 24 h).

PRESENTATION – Clear glass vials (2 ml) and clear glass ampules (2 ml), equivalent to 100 µg/ml base as solution for i.v. infusion.

PROPRIETARY NAME – *Precedex* (US).

SOURCES – Abbott; Orion Corporation.

RECENT REFERENCES

- Baughman, V.L. et al. *Pharmacokinetic/pharmacodynamic effects of dexmedetomidine in patients with hepatic failure.* Anesth Analg 2000, 90(2, Suppl. S): Abst S-391.
- Bol, C.J.J.G. et al. *Anesthetic profile of dexmedetomidine identified by stimulus-response and continuous measurements in rats.* J Pharmacol Exp Ther 1999, 291(1): 153.
- Cunningham, F.E. et al. *Pharmacokinetics of dexmedetomidine (DEX) in patients with hepatic failure (HF).* Annu Meet Am Soc Clin Pharmacol Ther (March 18-20, San Antonio) 1999, Abst PI-45.
- Dutta, S. et al. *Dexmedetomidine pharmacokinetics in a human maximum tolerated dose study.* Annu Meet Am Assoc Pharm Sci (Nov 14-18, New Orleans) 1999, Abst 2013.
- Dutta, S. et al. *Dexmedetomidine-propofol pharmacodynamic interaction in healthy volunteers.* Annu Meet Am Assoc Pharm Sci (Nov 14-18, New Orleans) 1999, Abst 2050.
- Farber, N.E. et al. *Dexmedetomidine modulates cardiovascular responses to stimulation of central nervous system pressor sites.* Anesth Analg 1999, 88(3): 617.
- Fragen, R.J. and Fitzgerald, P.C. *Effect of dexmedetomidine on the minimum alveolar concentration (MAC) of sevoflurane in adults age 55 to 70 years.* J Clin Anesth 1999, 11(6): 466.
- Fu, W. and White, P.F. *Dexmedetomidine failed to block the acute hyperdynamic response to electroconvulsive therapy.* Anesthesiology 1999, 90(2): 422.
- Jolkkonen, J. et al. *Neuroprotection by the α₂-adrenoceptor agonist, dexmedetomidine, in rat focal cerebral ischemia.* Eur J Pharmacol 1999, 372(1): 31.
- Khan, Z.P. et al. *Effects of dexmedetomidine on isoflurane requirements in healthy volunteers. 1: Pharmacodynamic and pharmacokinetic interactions.* Br J Anaesth 1999, 83(3): 372.
- Mantz, J. *Dexmedetomidine.* Drugs Today 1999, 35(3): 151.
- Nishina, K. et al. *The effects of clonidine and dexmedetomidine on human neutrophil functions.* Anesth Analg 1999, 88(2): 452.
- Ohata, H. et al. *Intravenous dexmedetomidine inhibits cerebrovascular dilation induced by isoflurane and sevoflurane in dogs.* Anesth Analg 1999, 89(2): 370.

SOURCE – Akzo Nobel.

REFERENCES

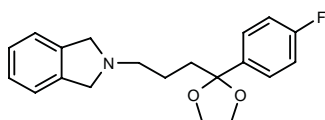
1. Hamilton, N.M. (Akzo Nobel N.V.) *α-Amino acid phenyl ester derivs.* WO 0005196.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

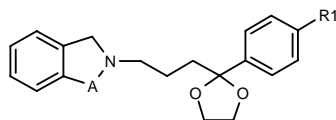
285055

2-[3-[2-(4-Fluorophenyl)-1,3-dioxolan-2-yl]propyl]-2,3-dihydro-1*H*-isoindole



C20 H22 F N O2; Mol wt: 327.3968

ACTION – Agent for the treatment of CNS disorders such as sleep disorders, anxiety, depression and schizophrenia, a 5-HT₇ receptor antagonist. Other bicyclic compounds include the following:



Compound	R1	A	Formula
285056	Br	-CH2-	C ₂₀ H ₂₂ BrNO ₂
285057	Me	-CH2-	C ₂₁ H ₂₅ NO ₂
285058	F	-(CH2)2-	C ₂₁ H ₂₄ FNO ₂

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Cain, G.A. and McElroy, J.F. (DuPont Pharmaceuticals Co.) *5-HT₇ receptor antagonists.* WO 0000472.

DEXMEDETOMIDINE* HYDROCHLORIDE

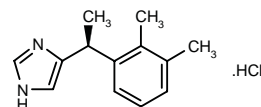
Rec INN; BANM; USAN

145584

(+)-4-[(*S*)-α,2,3-Trimethylbenzyl]imidazole monohydrochloride

(+)-(*S*)-4-[1-(2,3-Dimethylphenyl)ethyl]-1*H*-imidazole monohydrochloride

MPV-1440



C13 H16 N2 . HCl; Mol wt: 236.7443

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PROPRIETARY NAME – *Precedex* (US).

SOURCES – Abbott; Orion Corporation.

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- Baughman, V.L. et al. *Pharmacokinetic/pharmacodynamic effects of dexmedetomidine in patients with hepatic failure.* Anesth Analg 2000, 90(2, Suppl. S): Abst S-391.
- Bol, C.J.J.G. et al. *Anesthetic profile of dexmedetomidine identified by stimulus-response and continuous measurements in rats.* J Pharmacol Exp Ther 1999, 291(1): 153.
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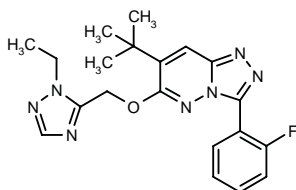
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*See **Medetomidine** Drug Data Rep 1991, 013(10): 0832.

ANXIOLYTICS

284911

7-*tert*-Butyl-6-(1-ethyl-1*H*-1,2,4-triazol-5-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine



C20 H22 F N7 O; Mol wt: 395.4398

ACTION – Anxiolytic agent with selective affinity for the α_2 and/or α_3 subunits of the human GABA_A receptor relative to the α_1 subunit, reported to possess good oral bioavailability and to be substantially non-sedating. Compound gave K_i values for displacement of [³H]-flumazenil binding from the α_2 and/or α_3 subunit of the human GABA_A receptor stably expressed in murine fibroblast Ltk- cells of less than 1 nM. It is reported to exhibit anxiolytic activity in the elevated plus maze and conditioned suppression of drinking tests.

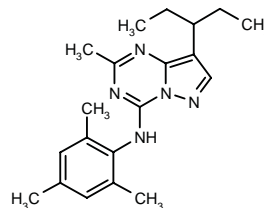
SOURCE – Merck Sharp & Dohme.

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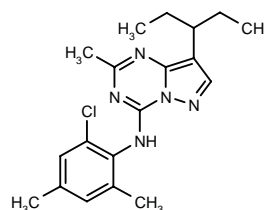
284913

N-[8-(1-Ethylpropyl)-2-methylpyrazolo[1,5-*a*][1,3,5]triazin-4-yl]-*N*-(2,4,6-trimethylphenyl)amine



C20 H27 N5; Mol wt: 337.4683

ACTION – Corticotropin-releasing factor (CRF) antagonist claimed for the treatment of affective disorder, anxiety, depression, posttraumatic stress disorder, supranuclear palsy, epilepsy, stroke, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal disorders, eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders, cardiovascular disorders, obesity or fertility disorders. Another compound from this series of pyrazolo[1,5-*a*]triazines is:



284914: C19 H24 Cl N5

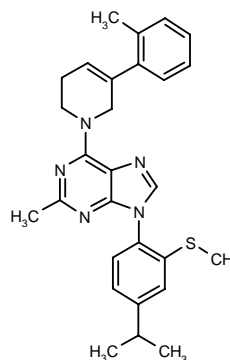
SOURCE – DuPont Pharmaceuticals.

REFERENCES

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285087

2-Methyl-9-[4-isopropyl-2-(methylsulfonyl)phenyl]-6-[5-(2-methylphenyl)-1,2,3,6-tetrahydropyridin-1-yl]-9*H*-purine



C28 H31 N5 S; Mol wt: 469.6539

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist (IC_{50} = 20.19 nM against [^{125}I]-CRF binding in rat frontal cortex membranes) with potential in the treatment of depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorders, hypertension, gastrointestinal disorders, drug dependence, epilepsy, cerebral infarction, ischemia and edema, head injury, inflammation and immune-related diseases. A representative compound from a series of aryltetrahydropyridine derivatives.

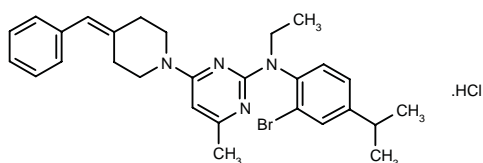
SOURCE – Taisho.

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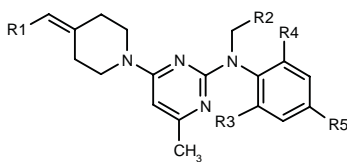
285104

N-[4-[4-(Benzylidene)piperidin-1-yl]-6-methylpyrimidin-2-yl]-*N*-(2-bromo-4-isopropylphenyl)-*N*-ethylamine hydrochloride



C28 H33 Br N4 . HCl; Mol wt: 541.9616

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist (IC_{50} = 282.6 nM against [^{125}I]-CRF binding in rat frontal cortex membranes) with potential in the treatment of anxiety, depression, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorders, hypertension, gastrointestinal disorders, drug dependence, epilepsy, cerebral infarction, ischemia and edema, head injury, inflammation and immune-related diseases. A representative compound from a series of arylmethylidenepiperidinopyrimidine derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
285105	1-Naph	ethynyl	Me	Me	Me	C ₃₃ H ₃₄ N ₄
285106	3-F-Ph	cyclobutyl	Br	H	N(Me) ₂	C ₃₀ H ₃₅ BrFN ₅

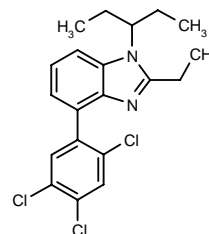
SOURCE – Taisho.

REFERENCES

1. Nakazato, A. et al. (Taisho Pharmaceutical Co., Ltd.) *Arylmethylenepiperidinopyrimidine derivs.* JP 1999335373.

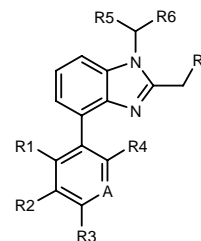
285273

2-Ethyl-1-(1-ethylpropyl)-4-(2,4,5-trichlorophenyl)-1*H*-benzimidazole



C20 H21 Cl₃ N₂; Mol wt: 395.7589

ACTION – Corticotropin-releasing factor (CRF) antagonist with potential in the treatment of psychiatric and neurological disorders such as depression, affective disorders and anxiety. Other specifically claimed compounds within this series of benzimidazole derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	A	Formula
285274	H	Cl	Cl	Cl	Me	Pr	H	CH	C ₁₉ H ₁₉ Cl ₃ N ₂
285275	H	Cl	Cl	Cl	cyclopropyl	cyclopropyl	Me	CH	C ₂₂ H ₂₁ Cl ₃ N ₂
285276	H	Cl	Cl	Cl	Et	Ph	Me	CH	C ₂₄ H ₂₁ Cl ₃ N ₂
285277	H	H	OMe	Me	cyclopropyl	cyclopropyl	Me	CH	C ₂₄ H ₂₈ N ₂ O
285278	Me	H	Me	Me	-(CH ₂) ₄ -		Me	N	C ₂₂ H ₂₇ N ₃

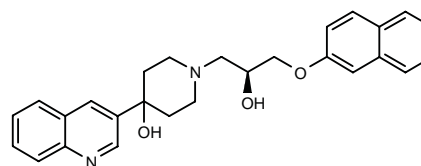
SOURCE – DuPont Pharmaceuticals.

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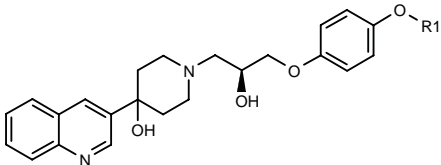
285508

1-[2(*S*)-Hydroxy-3-(2-naphthyloxy)propyl]-4-(3-quinolinyl)-piperidin-4-ol



C27 H28 N₂ O₃; Mol wt: 428.5292

ACTION – 5-HT_{1f} receptor antagonist with potential in the treatment of anxiety disorders such as panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, specific phobia, social phobia and generalized anxiety disorder. Anxiolytic activity was demonstrated by its ability to significantly increase social interaction time compared to baseline in rats when given at a dose of 20 mg/kg i.p. A representative compound from a series of substituted piperidine derivatives, wherein the following are also included:



Compound	R1	Formula
285509	CF3	C ₂₄ H ₂₅ F ₃ N ₂ O ₄
285510	Ph	C ₂₉ H ₃₀ N ₂ O ₄

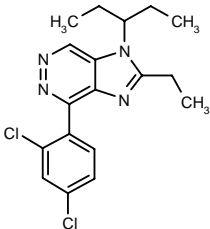
SOURCE – Lilly.

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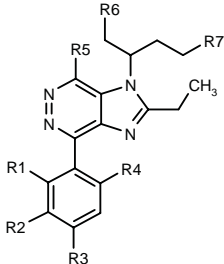
285728

4-(2,4-Dichlorophenyl)-2-ethyl-1-(1-ethylpropyl)-1H-imidazo[4,5-d]pyridazine



C₁₈ H₂₀ Cl₂ N₄; Mol wt: 363.2900

ACTION – Corticotropin-releasing factor (CRF) antagonist with potential in the treatment of psychiatric and neurological disorders such as depression, affective disorders and anxiety. Other compounds within this series of imidazo-pyridines, -pyridazines and -triazines include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	Formula
285730	Me	H	Me	Me	H	Me	H	C ₂₁ H ₂₈ N ₄
285731	H	F	Cl	Cl	H	Me	H	C ₁₈ H ₁₉ Cl ₂ FN ₄
285733	Cl	H	Cl	H	Me	Me	H	C ₁₉ H ₂₂ Cl ₂ N ₄
285734	Cl	H	Cl	H	OPr	Me	H	C ₂₁ H ₂₆ Cl ₂ N ₄ O
285735	Cl	H	Cl	H	Cl	H	Me	C ₁₈ H ₁₉ Cl ₃ N ₄
285736	Cl	H	Cl	H	OMe	H	Me	C ₁₉ H ₂₂ Cl ₂ N ₄ O

SOURCE – DuPont Pharmaceuticals.

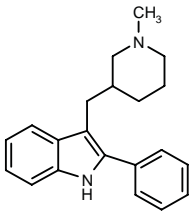
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ANTIPSYCHOTIC DRUGS

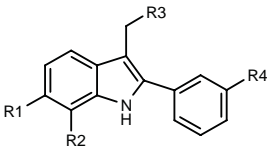
285707

3-(1-Methylpiperidin-3-ylmethyl)-2-phenyl-1H-indole



C₂₁ H₂₄ N₂; Mol wt: 304.4346

ACTION – Agent for the treatment of CNS disorders, particularly schizophrenia and psychotic disorders, a selective human 5-HT_{2A} receptor antagonist. Other specifically claimed compounds from this series of phenylindole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
285708	H	H	2-Me-2-azabicyclo-[2.2.2]oct-3-yl	H	C ₂₃ H ₂₆ N ₂
285709	H	Cl	(S)-1,4-(Me)2-2-Piz	H	C ₂₁ H ₂₄ ClN ₃
285710	H	H	(R)-1-Me-2-Pip	H	C ₂₁ H ₂₄ N ₂
285711	H	H	1-(PhCH ₂)-2-Pip	H	C ₂₇ H ₂₈ N ₂
285712	F	H	(S)-1-Me-2-Piz	F	C ₂₀ H ₂₁ F ₂ N ₃

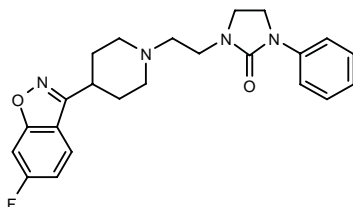
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Moyes, C.R. and Rowley, M. (Merck Sharp & Dohme Ltd.) Phenylindole derivs. as 5-HT_{2A} receptor ligands. WO 0005229.

S-18327***266085**

1-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-3-phenylimidazolidin-2-one



C23 H25 F N4 O2; Mol wt: 408.4745

ACTION – Potential atypical antipsychotic agent with particularly high affinity for human α_{1A} -adrenoceptors, 5-HT_{2A} receptors and dopamine D₄ receptors (pK_i = 9.0, 8.5 and 8.1, respectively), and lower affinity for human D₁, D₂, D₃, 5-HT_{1A}, 5-HT_{1C} receptors and α_{2A} -adrenoceptors (pK_i = 6.4-7.4); it also exhibits moderate affinity for histamine H₁ receptors (pK_i = 7.7) and low affinity for human muscarinic M₁ receptors (pK_i = 6.3). Potent antagonist activity at α_1 -adrenoceptors, D₄ and 5-HT_{2A} receptors was seen, and less pronounced antagonist activity at α_2 -adrenoceptors, D₂ and D₁ receptors. Overall, it showed a profile similar to that of clozapine, except for its moderate or weak affinity for muscarinic and histamine receptors. Blockade of α_2 -adrenoceptors by compound results in enhanced adrenergic transmission and facilitates frontocortical dopaminergic transmission, while α_1 -adrenoceptor blockade contributes to inhibition of dorsal raphe-derived serotonergic pathways. *In vivo*, it inhibited apomorphine-induced climbing in mice (ID₅₀ = 0.2 mg/kg s.c.), cocaine- and amphetamine-induced hyperlocomotion in rats (ID₅₀ = 0.7 and 1.3 mg/kg s.c., respectively), a conditioned avoidance response in rats (ID₅₀ = 0.8 mg/kg s.c.), phencyclidine-induced locomotion in rats (ID₅₀ = 0.1 mg/kg s.c.), DOI-induced head twitches in rats (ID₅₀ = 0.1 mg/kg s.c.) and dizocilpine-induced hyperlocomotion and spontaneous tail flicks in rats (ID₅₀ = 0.9 and 1.7 mg/kg s.c., respectively). The compound also generalized to a clozapine discriminative stimulus in rats, evoked latent inhibition in rats, inhibited isolation-induced aggression in mice and displayed anxiolytic-like activity in several rat models, whereas activity in models predictive of extrapyramidal side effects (e.g., induction of catalepsy in rats and inhibition of methylphenidate-induced gnawing in rats) was observed only at markedly higher doses. Potent oral activity was also seen in models of both antipsychotic and anxiolytic activity. Compound is now undergoing clinical evaluation as a potential treatment for schizophrenia.

SOURCE – Servier.**REFERENCES**

- Peglion, J.-L. et al. (ADIR et Cie.) 3-(Piperid-4-yl)-1,2-benzisoxazole and 3-(piperazin-4-yl)-1,2-benzisoxazole cpds. EP 0811622, FR 2749304, US 5780474.
- Brocco, M. et al. Influence of S18327, clozapine and other antipsychotics upon dizocilpine (DIZ)-induced spontaneous tail-flicks (STFSs) in rats in relation to their action at multiple monoaminergic receptors. Behav Pharmacol 1999, 10(Suppl. 1): S13.
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4. Millan, M.J. et al. S 18327, a novel phenylimidazolinone and potential antipsychotic: Antagonist properties at α_2 -adrenergic (AR) receptors in vitro and in vivo. Eur Neuropsychopharmacol 1999, 9(Suppl. 5): Abst P.2.020.

5. Millan, M.J. et al. S 18327, a novel, phenylimidazolinone antipsychotic agent I: receptor profile in comparison to haloperidol, clozapine, Seroquel and olanzapine. Soc Neurosci Abst 1997, 23(1-2): Abst 747.16.

6. Millan, M.J. et al. S18327 (1-[2-[4-(6-fluoro-1, 2-benzisoxazol-3-yl)piperid-1-yl]ethyl]-3-phenyl imidazolin-2-one), a novel, potential antipsychotic displaying marked antagonist properties at α_1 - and α_2 -adrenergic receptors: I. Receptorial, neurochemical, and electrophysiological profile. J Pharmacol Exp Ther 2000, 292(1): 38.

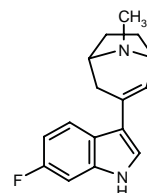
7. Millan, M.J. et al. S18327 (1-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperid-1-yl]ethyl]-3-phenyl imidazolin-2-one), a novel, potential antipsychotic displaying marked antagonist properties at α_1 - and α_2 -adrenergic receptors: II. Functional profile and a multi-parametric comparison with haloperidol, clozapine, and 11 other antipsychotic agents. J Pharmacol Exp Ther 2000, 292(1): 54.

*Identified compound **266085** Drug Data Rep 1998, 020(08): 0662.

TREATMENT OF MOOD DISORDERS

284373

6-Fluoro-3-(8-methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-1H-indole



C16 H17 F N2; Mol wt: 256.3223

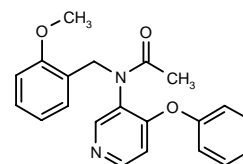
ACTION – 5-HT reuptake inhibitor with potential in the treatment of depression, obsessive-compulsive disorder and obesity, a representative compound from a series of 3-substituted 8-azabicyclo[3.2.1]oct-2-enes and 8-azabicyclo[3.2.1]octanes.

SOURCE – Lilly.**REFERENCES**

- Audia, J.E. et al. (Eli Lilly and Company) Inhibition of serotonin reuptake. EP 0969005, WO 9965492.

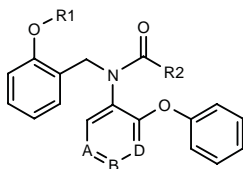
285406

N-(2-Methoxybenzyl)-N-[4-(phenoxy)pyridin-3-yl]-acetamide



C21 H20 N2 O3; Mol wt: 348.4000

ACTION – Agent with high affinity for the mitochondrial diazepam binding inhibitor (DBI) receptor (MDR), as demonstrated in a binding assay by an IC_{50} value of 0.658 nM for inhibition of [3H]-PK-11195 binding in rat cerebral cortex mitochondrial preparations. Potentially useful in the treatment of depression, epilepsy, sleep disorders, cognitive disorders, schizophrenia, motor, eating and circulatory disorders, drug dependence, cancer, disorders of lipid metabolism, cerebral infarction, AIDS, Alzheimer's disease and Huntington's chorea. Other compounds within this series of aryloxy-substituted nitrogen-containing arylamine derivatives include the following:



Compound	R1	R2	A	B	D	Formula
285407	Et	Me	N	CH	CH	C ₂₂ H ₂₂ N ₂ O ₃
285408	i-Pr	Me	N	CH	CH	C ₂₃ H ₂₄ N ₂ O ₃
285409	Et	NHMe	N	CH	CH	C ₂₂ H ₂₃ N ₃ O ₃
285410	Me	Me	CH	CH	N	C ₂₁ H ₂₀ N ₂ O ₃
285411	Me	Me	CH	N	CH	C ₂₁ H ₂₀ N ₂ O ₃

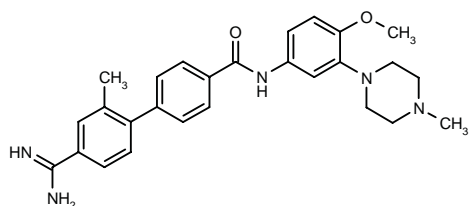
SOURCES – Nihon Nohyaku; Taisho.

REFERENCES

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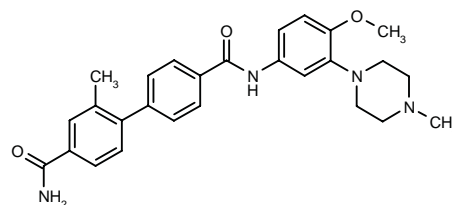
285414

4'-Amidino-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2'-methylbiphenyl-4-carboxamide



C₂₇ H₃₁ N₅ O₂; Mol wt: 457.5749

ACTION – Potent and selective 5-HT_{1B} and 5-HT_{1D} receptor antagonist (IC_{50} = 0.5 and 3 nM, respectively) with moderate affinity for 5-HT_{1A} receptors (IC_{50} = 23 nM) and functional antagonist activity in rabbit saphenous vein (pA_2 = 9.6). Compound showed weak 5-HT reuptake-inhibitory activity (IC_{50} = 407 nM) and was able to antagonize the sumatriptan-induced inhibition of K⁺-evoked 5-HT release from guinea pig cortex slices. Potentially useful for the treatment of depressive syndromes including obsessive-compulsive disorder. Another related compound is:



285413: C₂₇ H₃₀ N₄ O₃

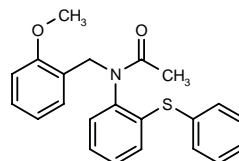
SOURCE – Merck KGaA.

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- Liao, Y. et al. New selective and potent 5-HT_{1B/1D} antagonists: Chemistry and pharmacological evaluation of *N*-piperazinylphenyl biphenylcarboxamides and biphenylsulfonamides. J Med Chem 2000, 43(3): 517.

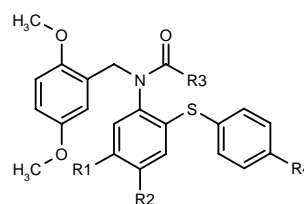
285415

N-(2-Methoxybenzyl)-*N*-[2-(phenylsulfonyl)phenyl]-acetamide

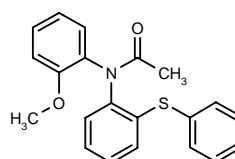


C₂₂ H₂₁ N O₂ S; Mol wt: 363.4789

ACTION – Agent with high affinity for the mitochondrial DBI (diazepam binding inhibitor) receptor (MDR; IC_{50} = 1.67 nM in rat cortex mitochondrial preparations), with potential in the treatment of anxiety, depression, epilepsy, sleep disorders, cognition disorders, schizophrenia, motor disorders, eating disorders, circulatory disorders, drug dependence, cancer, lipid metabolism disorders, cerebral infarction, AIDS, Alzheimer's disease and Huntington's chorea. Other compounds within this series of arylthioanilide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
285416	Me	H	Me	F	C ₂₄ H ₂₄ FNO ₃ S
285417	Me	H	Me	OMe	C ₂₅ H ₂₇ NO ₄ S
285418	H	Cl	Me	H	C ₂₃ H ₂₂ ClNO ₃ S
285419	H	Cl	Me	F	C ₂₃ H ₂₁ ClFNO ₃ S
285420	H	Cl	NHMe	F	C ₂₃ H ₂₂ ClFN ₂ O ₃ S



285421: C₂₁ H₁₉ N O₂ S

SOURCES – Nihon Nohyaku; Taisho.

REFERENCES

1. Nagamine, M. et al. (Nihon Nohyaku Co., Ltd.; Taisho Pharmaceutical Co., Ltd.) *Arylthioaniline derivs.* JP 2000001470.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

CONANTOKIN-R

284922

Glycyl-L-glutamyl-4-carboxy-L-glutamyl-4-carboxy-L-glutamyl-L-valyl-L-alanyl-L-lysyl-L-methionyl-L-alanyl-L-alanyl-4-carboxy-L-glutamyl-L-leucyl-L-alanyl-L-arginyl-4-carboxy-L-glutamyl-L-asparaginy-L-isoleucyl-L-alanyl-L-lysyl-glycyl-L-cysteinyl-L-lysyl-L-valyl-L-asparaginy-L-cysteinyl-L-tyrosyl-L-proline cyclic (21-25)-disulfide

C127 H201 N35 O49 S3; Mol wt: 3098.3790

ACTION – Potent NMDA receptor antagonist extracted from the venom of the snail *Conus radiatus*, proven to block glutamate-evoked currents in *Xenopus* oocytes expressing NMDA receptors containing both NR2B and NR2A subunits at low micromolar concentrations, and at higher concentrations to block NMDA receptors containing the NR2C subunit; compound was inactive in oocytes expressing the AMPA receptor subunit GluR1 or the kainate receptor subunit GluR6. In mouse cortical neurons, compound blocked inward currents evoked by NMDA ($IC_{50} = 350$ nM), but not by GABA or kainate. In mice, intracerebroventricular (i.c.v.) administration at subtoxic doses was associated with a strong protective effect against audiogenic seizures ($ED_{50} = 0.013$ nmol) and tonic extension induced by maximal and threshold electroshock stimulation ($ED_{50} = 0.082$ and 0.085 nmol, respectively), and it partially blocked clonic seizures induced by pentylenetetrazol (50% maximal protection at 0.10 nmol). Compound showed a different pharmacological profile than the NMDA receptor antagonist MK-801 (dizocilpine), having > 10-fold lower affinity *in vitro*, but being more than 1 order of magnitude more potent *in vivo*. Potentially useful as an antiepileptic agent.

SOURCES – Cognetix; CytoTherapeutics; University of Utah, Salt Lake City, UT (US).

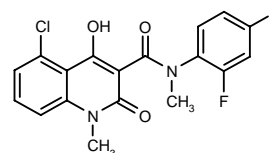
REFERENCES

1. Abogadie, F.C. et al. (University of Utah; Cognetix, Inc.) *Conantokins*. WO 9803541.
2. McCabe, R.T. et al. (Cognetix, Inc.) *Use of conantokins*. WO 9803189.
3. Saydoff, J. (CytoTherapeutics, Inc.) *Use of conantokins for producing analgesia or for neuroprotection*. WO 9848821.
4. White, H.S. et al. *In vitro and in vivo characterization of conantokin-R, a selective NMDA receptor antagonist isolated from the venom of the fish-hunting snail Conus radiatus*. J Pharmacol Exp Ther 2000, 292(1): 425.
5. *CytoTherapeutics and Cognetix collaborate on CNS R&D*. DailyDrugNews.com (Daily Essentials) 1997, Feb 24.

THERAPY OF IMMUNOLOGIC NEUROMUSCULAR DISORDERS

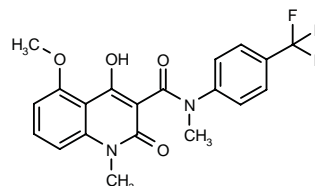
285382

5-Chloro-N-(2,4-difluorophenyl)-4-hydroxy-N,1-dimethyl-2-oxo-1,2-dihydroquinoline-3-carboxamide



C18 H13 Cl F2 N2 O3; Mol wt: 378.7607

ACTION – Agent for the treatment of autoimmune diseases and inflammatory disorders, particularly multiple sclerosis and its manifestations, an analogue of roquinimex found to exhibit improved activity and reduced side effects. Compound exhibited significant activity in mice with acute experimental autoimmune encephalomyelitis (aEAE), giving 59 and 96% inhibition at 0.2 and 1 mg/kg p.o., respectively, and being superior to roquinimex, which is reported to exhibit > 50% inhibition only at doses of 5 mg/kg p.o. or higher. Contrary to parent compound, it was nonteratogenic in rats. Another compound from this series of quinoline derivatives is:



285383: C20 H17 F3 N2 O4

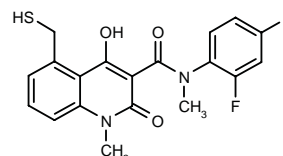
SOURCE – Active Biotech.

REFERENCES

1. Björk, A. et al. (Active Biotech AB) *Quinoline derivs.* WO 0003991.

285385

N-(2,4-Difluorophenyl)-4-hydroxy-N,1-dimethyl-2-oxo-5-(sulfanylmethyl)-1,2-dihydroquinoline-3-carboxamide



C19 H16 F2 N2 O3 S; Mol wt: 390.4084

SOURCES – Nihon Nohyaku; Taisho.

REFERENCES

1. Nagamine, M. et al. (Nihon Nohyaku Co., Ltd.; Taisho Pharmaceutical Co., Ltd.) *Arylthioaniline derivs.* JP 2000001470.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

CONANTOKIN-R

284922

Glycyl-L-glutamyl-4-carboxy-L-glutamyl-4-carboxy-L-glutamyl-L-valyl-L-alanyl-L-lysyl-L-methionyl-L-alanyl-L-alanyl-4-carboxy-L-glutamyl-L-leucyl-L-alanyl-L-arginyl-4-carboxy-L-glutamyl-L-asparaginy-L-isoleucyl-L-alanyl-L-lysyl-glycyl-L-cysteinyl-L-lysyl-L-valyl-L-asparaginy-L-cysteinyl-L-tyrosyl-L-proline cyclic (21-25)-disulfide

C127 H201 N35 O49 S3; Mol wt: 3098.3790

ACTION – Potent NMDA receptor antagonist extracted from the venom of the snail *Conus radiatus*, proven to block glutamate-evoked currents in *Xenopus* oocytes expressing NMDA receptors containing both NR2B and NR2A subunits at low micromolar concentrations, and at higher concentrations to block NMDA receptors containing the NR2C subunit; compound was inactive in oocytes expressing the AMPA receptor subunit GluR1 or the kainate receptor subunit GluR6. In mouse cortical neurons, compound blocked inward currents evoked by NMDA ($IC_{50} = 350$ nM), but not by GABA or kainate. In mice, intracerebroventricular (i.c.v.) administration at subtoxic doses was associated with a strong protective effect against audiogenic seizures ($ED_{50} = 0.013$ nmol) and tonic extension induced by maximal and threshold electroshock stimulation ($ED_{50} = 0.082$ and 0.085 nmol, respectively), and it partially blocked clonic seizures induced by pentylenetetrazol (50% maximal protection at 0.10 nmol). Compound showed a different pharmacological profile than the NMDA receptor antagonist MK-801 (dizocilpine), having > 10-fold lower affinity *in vitro*, but being more than 1 order of magnitude more potent *in vivo*. Potentially useful as an antiepileptic agent.

SOURCES – Cognetix; CytoTherapeutics; University of Utah, Salt Lake City, UT (US).

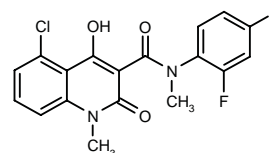
REFERENCES

1. Abogadie, F.C. et al. (University of Utah; Cognetix, Inc.) *Conantokins*. WO 9803541.
2. McCabe, R.T. et al. (Cognetix, Inc.) *Use of conantokins*. WO 9803189.
3. Saydoff, J. (CytoTherapeutics, Inc.) *Use of conantokins for producing analgesia or for neuroprotection*. WO 9848821.
4. White, H.S. et al. *In vitro and in vivo characterization of conantokin-R, a selective NMDA receptor antagonist isolated from the venom of the fish-hunting snail Conus radiatus*. J Pharmacol Exp Ther 2000, 292(1): 425.
5. *CytoTherapeutics and Cognetix collaborate on CNS R&D*. DailyDrugNews.com (Daily Essentials) 1997, Feb 24.

THERAPY OF IMMUNOLOGIC NEUROMUSCULAR DISORDERS

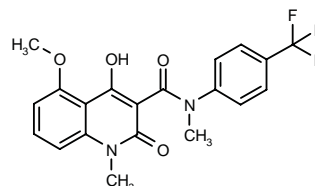
285382

5-Chloro-N-(2,4-difluorophenyl)-4-hydroxy-N,1-dimethyl-2-oxo-1,2-dihydroquinoline-3-carboxamide



C18 H13 Cl F2 N2 O3; Mol wt: 378.7607

ACTION – Agent for the treatment of autoimmune diseases and inflammatory disorders, particularly multiple sclerosis and its manifestations, an analogue of roquinimex found to exhibit improved activity and reduced side effects. Compound exhibited significant activity in mice with acute experimental autoimmune encephalomyelitis (aEAE), giving 59 and 96% inhibition at 0.2 and 1 mg/kg p.o., respectively, and being superior to roquinimex, which is reported to exhibit > 50% inhibition only at doses of 5 mg/kg p.o. or higher. Contrary to parent compound, it was nonteratogenic in rats. Another compound from this series of quinoline derivatives is:



285383: C20 H17 F3 N2 O4

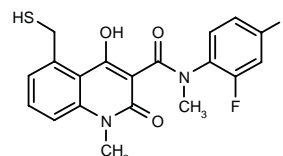
SOURCE – Active Biotech.

REFERENCES

1. Björk, A. et al. (Active Biotech AB) *Quinoline derivs.* WO 0003991.

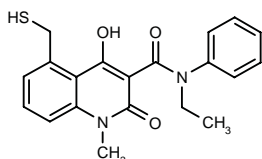
285385

N-(2,4-Difluorophenyl)-4-hydroxy-N,1-dimethyl-2-oxo-5-(sulfanylmethyl)-1,2-dihydroquinoline-3-carboxamide



C19 H16 F2 N2 O3 S; Mol wt: 390.4084

ACTION – Agent for the treatment of autoimmune diseases and inflammatory disorders, particularly multiple sclerosis and its manifestations, an analogue of roquinimex that was found to exhibit improved activity and reduced side effects. Compound exhibited significant activity in mice with acute experimental autoimmune encephalomyelitis (EAE), giving 67 and 97% inhibition at 0.2 and 1 mg/kg p.o., respectively, and being superior to roquinimex, which is reported to exhibit > 50% inhibition only at doses of 5 mg/kg p.o. or higher. Contrary to parent compound, it was found to be nonteratogenic in rats. Another compound from this series of quinoline derivatives is:



285387: C20 H20 N2 O3 S

SOURCE – Active Biotech.

REFERENCES

1. Björk, A. et al. (Active Biotech AB) *Quinoline derivs.* WO 0003992.

ANTISPASTIC DRUGS AND DRUGS FOR MUSCLE SPASMS

BOTULINUM TOXIN TYPE B

215951

AN072

BoNT/B

BotB™ (former brand name)

Neurobloc™

ACTION – Botulinum toxin type B proven to inhibit acetylcholine release from presynaptic nerve terminals at the neuromuscular junction by cleaving the vesicle-associated membrane protein synaptobrevin. Preliminary safety and efficacy studies in patients with cervical dystonia indicated that compound was safe and well tolerated at doses of 300-12,000 U, and induced significant clinical improvement at the higher doses. In a 16-week, multicenter, double-blind, placebo-controlled trial in botulinum toxin type A-responsive patients, compound (5000 and 10,000 U) showed significant improvement in clinical symptoms compared with placebo, with a slight increase in side effects noted in the higher dose group. The duration of effect for both doses was estimated to be 12-16 weeks and selflimiting side effects of dry mouth and dysphagia were reported. Another trial of similar design tested compound as a single dose of 10,000 U versus placebo in type A-resistant patients. Similar efficacy and safety results were obtained. Compound is undergoing FDA review.

SOURCES – Athena Neurosciences; Axogen; Draxis Health; Elan.

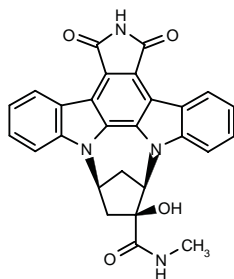
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2. Brashear, A. et al. *Safety and efficacy of Neurobloc(TM) (botulinum toxin type-B) in type-A responsive cervical dystonia patients.* Neurology 1999, 52(6, Suppl. 2): Abst S46.003.
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4. Brin, M.F. et al. *Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia.* Neurology 1999, 53(7): 1431.
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7. Lew, M.F. et al. *Botulinum toxin type B: A double-blind, placebo-controlled, safety and efficacy study in cervical dystonia.* Neurology 1997, 49(3): 701.
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12. Athena Neurosciences, Inc. *completes three phase I clinical trials for botulinum toxin type B.* Athena Neurosciences, Inc. Press Release 1994, May 4.
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14. Athena Neurosciences, Inc. *reports financial results for fiscal 1994, fourth quarter.* Athena Neurosciences, Inc. Press Release 1995, Feb 13.
15. Athena Neurosciences, Inc. *reports financial results for fiscal 1995 and fourth quarter.* Athena Neurosciences, Inc. Press Release 1996, Feb 8.
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20. Two Elan neurology products move closer to market in U.S.. DailyDrugNews.com (Daily Essentials) 1999, Jan 12.
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COGNITION-ENHANCING DRUGS

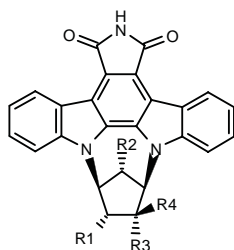
285059

(9*R*,10*S*,12*S*)-10-Hydroxy-*N*-methyl-1,3-dioxo-2,3,9,10,11,12-hexahydro-1*H*-9,12-methanodiindolo-[1,2,3-*fg*:3',2',1'-*kl*]pyrrolo[3,4-*l*][1,6]benzodiazocine-10-carboxamide



C₂₇ H₂₀ N₄ O₄; Mol wt: 464.4790

ACTION – Agent for the treatment of dementias characterized by tau hyperphosphorylation such as Alzheimer's disease, as well as for the treatment of cancer, that acts by inhibiting ERK2 and cdk, particularly cdc2, kinase activity. *In vitro*, compound was shown to inhibit ERK2 (PK40), cdc2, protein kinase A (PKA) and protein kinase C (PKC) activity with IC₅₀ values of 0.044, 0.044, 0.65 and 0.65 μM, respectively. Compound was also shown to inhibit ERK2 activation of tau hyperphosphorylation in SY5Y cells and tau hyperphosphorylation in rat hippocampal brain slices with respective IC₅₀ values of 0.58 and 0.18 μM. Other compounds from this series of indolocarbazole derivatives are:



Compound	R1	R2	R3	R4	Formula
285060	OH	OH	OH	H	C ₂₅ H ₁₇ N ₃ O ₅
285061	H	H	CO ₂ Me	OH	C ₂₇ H ₁₉ N ₃ O ₅

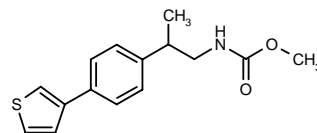
SOURCE – Bayer.

REFERENCES

1. Roder, H. et al. (Bayer Corp.) *Indolocarbazole derivs. useful for the treatment of neurodegenerative diseases and cancer*. US 6013646, WO 0001699.

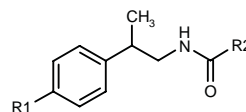
285532

N-[2-[4-(3-Thienyl)phenyl]propyl]carbamic acid methyl ester



C₁₅ H₁₇ N O₂ S; Mol wt: 275.3703

ACTION – Agent for the treatment of cognitive disorders, neurodegenerative disorders, age-related dementia or memory impairment, movement disorders, depression, attention deficit disorder, attention deficit hyperactivity disorder and psychosis that acts by potentiating glutamate receptor function. In particular, compound is reported to potentiate agonist-induced excitability of the human GluR4B receptor expressed in HEK293 cells, similarly to cyclothiazide, and is therefore expected to exhibit ampakine-like behavior. Other specifically claimed compounds from this series of amide, carbamate and urea derivatives include the following:



Compound	R1	R2	Formula
285533	3-thienyl	t-BuO	C ₁₈ H ₂₃ NO ₂ S
285534	3-thienyl	cyclohexyl-NH	C ₂₀ H ₂₆ N ₂ OS
285535	3-thienyl	NHCH ₂ Ph	C ₂₁ H ₂₂ N ₂ OS
285536	3-thienyl	2-furyl	C ₁₈ H ₁₇ NO ₂ S
285537	3-thienyl	4-morpholinyl	C ₁₈ H ₂₂ N ₂ O ₂ S
285539	4-(CO ₂ HCH ₂)-Ph	i-Pr	C ₂₁ H ₂₅ NO ₃
285540	4-CN-Ph	N(Et) ₂	C ₂₁ H ₂₅ N ₃ O

SOURCE – Lilly.

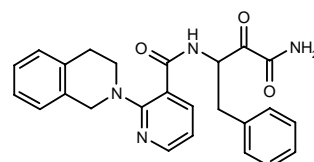
REFERENCES

1. Arnold, M.B. et al. (Eli Lilly and Company) *Amide, carbamate, and urea derivs. having glutamate receptor function potentiating activity*. EP 0976744, WO 0006156.

TREATMENT OF CEREBROVASCULAR DISEASES

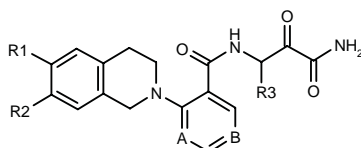
284024

N-(1-Benzyl-2-carbamoyl-2-oxoethyl)-2-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyridine-3-carboxamide



C₂₅ H₂₄ N₄ O₃; Mol wt: 428.4896

ACTION – An inhibitor of cysteine proteases such as calpain I and II and cathepsin B and L, reported to possess good water solubility and thus to be suitable for intravenous administration. Potentially useful in the treatment of neurodegenerative disorders, cerebral ischemia, stroke, Alzheimer's disease, Huntington's disease, epilepsy, cardiac or renal ischemia, rheumatoid arthritis, muscular dystrophy, restenosis, coronary or cerebral vasospasm, cataracts and cancer. A representative compound from a series of heterocyclically substituted amides, wherein the following are also included:



Compound	R1	R2	R3	A	B	Formula
284025	OMe	OMe	CH ₂ Ph	N	CH	C ₂₇ H ₂₈ N ₄ O ₅
284026	OMe	OMe	Bu	N	CH	C ₂₄ H ₃₀ N ₄ O ₅
284027	H	H	CH ₂ Ph	CH	CH	C ₂₆ H ₂₅ N ₃ O ₃
284028	H	H	CH ₂ Ph	CH	N	C ₂₅ H ₂₄ N ₄ O ₃

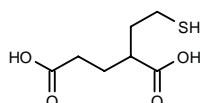
SOURCE – BASF.

REFERENCES

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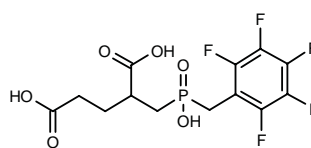
285205

2-(2-Sulfanylethyl)pentanedioic acid



C₇ H₁₂ O₄ S; Mol wt: 192.2338

ACTION – An inhibitor of *N*-acetylated α -linked acidic dipeptidase (NAALADase; K_i = 510 nM) found to protect against ischemic insult in cortical cell cultures with an EC₅₀ of 2 nM. Neuroprotective activity was also shown *in vivo* in a model of brain injury following middle cerebral artery occlusion (MCAO) in rats (52% protection when given at 3 mg/kg i.v. at 60 min postocclusion followed by 3 mg/kg/h for 4 h). In addition, compound exhibited analgesic activity in the acetic acid-induced writhing test in mice at 10 and 100 mg/kg i.p., as well as in a model of neuropathic pain in streptozotocin-diabetic rats at 10 mg/kg i.p., and it was shown to reduce phencyclidine (PCP)-induced locomotor activity in rats at 50 mg/kg i.p. Potentially useful in the treatment of stroke, Parkinson's disease, angiogenesis, compulsive disorders, prostate disorders, pain and diabetic neuropathy. Another specifically claimed compound is:



285206: C₁₃ H₁₂ F₅ O₆ P

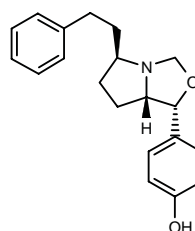
SOURCE – Guilford.

REFERENCES

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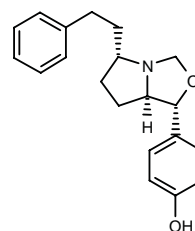
285217

4-[(1*R**,5*R**,7*aS**)-5-(2-Phenylethyl)perhydropyrrolo-[1,2-*c*]oxazol-1-yl]phenol



C₂₀ H₂₃ N O₂; Mol wt: 309.4067

ACTION – Agent for the treatment or prevention of diseases associated with overactivation of NMDA receptors including acute neurodegenerative disorders such as stroke and brain trauma, chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis, as well as schizophrenia, anxiety and depression, that acts as an antagonist at the NR2B subunit of the NMDA receptor, as demonstrated by an IC₅₀ value of 0.05 μ mol for inhibition of [³H]-Ro-25-6981 binding in rat brain membrane preparations. Another preferred compound is:



285218: C₂₀ H₂₃ N O₂

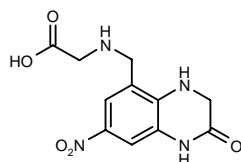
SOURCE – Roche.

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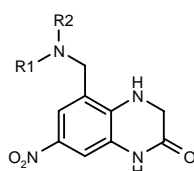
285230

2-(7-Nitro-2-oxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethyl-amino)acetic acid



C11 H12 N4 O5; Mol wt: 280.2388

ACTION – Neuroprotective agent, a glutamate receptor antagonist reported to possess greater aqueous solubility and better CNS penetration than structurally related compounds. Potentially useful for the treatment of stroke, cerebral ischemia, cerebral infarction, convulsions, hypoglycemia, anoxia, pain, Alzheimer's disease, Parkinson's disease and Huntington's disease. Other compounds from this series of substituted quinoxalin-2-one derivatives include the following:



Compound	R1	R2	Formula
285231		-(CH2)4-	C ₁₃ H ₁₆ N ₄ O ₃
285232	Ac	H	C ₁₂ H ₁₄ N ₄ O ₅
285233	CO ₂ Me	H	C ₁₁ H ₁₂ N ₄ O ₅
285234	CONHMe	H	C ₁₁ H ₁₃ N ₅ O ₄
285235	SO ₂ Me	H	C ₁₀ H ₁₂ N ₄ O ₅ S

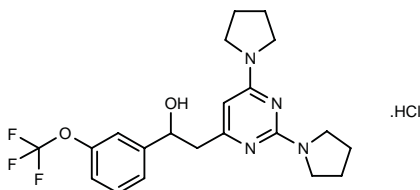
SOURCE – Warner-Lambert.

REFERENCES

1. Nikam, S.S. (Warner-Lambert Co.) *Subst. quinoxaline-2-ones as glutamate receptor antagonists*. US 6015800.

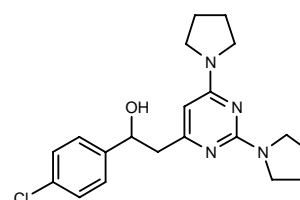
285322

2-[2,6-Di(1-pyrrolidinyl)pyrimidin-4-yl]-1-[3-(trifluoromethoxy)phenyl]ethanol hydrochloride



C21 H25 F3 N4 O2 . HCl; Mol wt: 458.9094

ACTION – Neuroprotective agent that blocks the activity of excitatory amino acids, particularly at the NMDA receptor complex, and has also been found to exhibit affinity for voltage-sensitive sodium channels. Compound was found to inhibit the binding of [³H]-ifenprodil to polyamine-sensitive sites in rat cerebral cortical membranes (IC₅₀ = 4.33 ± 1.56 μM; K_i = 1.40 ± 0.047 μM) and NMDA-induced cell death in murine neocortical neuron cultures (EC₅₀ = 1.7 μM). In addition, compound was shown to bind to voltage-sensitive sodium channels (IC₅₀ = 0.42 μM against [³H]-batrachotoxinin A 20-α-benzoate binding in rat brain homogenates) and to inhibit veratridine-induced toxicity in cultured murine cerebellar granule cells (EC₅₀ = 1.7 μM). Another compound from this series of arylalkylheterocyclic derivatives is:



285323: C20 H25 Cl N4 O

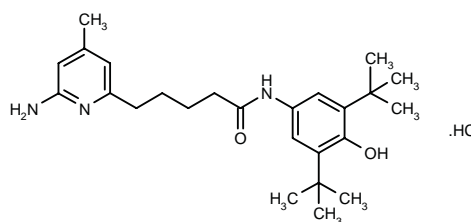
SOURCE – Monash University, Clayton (AU).

REFERENCES

1. Jarrott, B. et al. (Monash University) *Pharmaceutical agents*. WO 0002865.

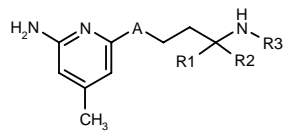
285324

5-(6-Amino-4-methylpyridin-2-yl)-N-(3,5-di-*tert*-butyl-4-hydroxyphenyl)pentanamide hydrochloride



C25 H37 N3 O2 . HCl ; Mol wt: 448.0472

ACTION – Agent for the treatment of cerebrovascular and cardiovascular disorders, central or peripheral nervous system disorders such as neurodegenerative disorders, proliferative, inflammatory and autoimmune diseases and transplant rejection, with nitric oxide synthase (NOS)-inhibitory activity and/or reactive oxygen species (ROS)-scavenging activity. *In vitro*, compound gave IC₅₀ values of less than 5 μM for inhibition of rat neuronal constitutive NOS and of less than 30 μM for inhibition of lipid peroxidation in rat cerebral cortex. Other specifically claimed compounds within this series of 2-aminopyridine derivatives include the following:



Compound	R1	R2	R3	A	Formula
285325	H	H	2,5-(OH)2-3-i-Pr-PhCO	-CH2-	C ₂₀ H ₂₇ N ₃ O ₃
285326	-O-		4-N(Me)2-Ph	-(CH2)3-	C ₂₀ H ₂₉ ClN ₄ O
285327	-O-		4-N(Me)2-Ph	-(CH2)2-	C ₁₉ H ₂₇ ClN ₄ O
285328	H	H	3-MeO-4-OH-PhCH=CHCH2	-CH2-	C ₂₀ H ₂₈ ClN ₃ O ₂
285330	H	H	2-OH-4,5-(MeO)2-PhCH2	-CH2-	C ₁₉ H ₂₇ N ₃ O ₃

SOURCE – SCRAS.

REFERENCES

1. Chabrier de Lassauniere, P.-E. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) 2-Aminopyridine derivs., their use as medicines and pharmaceutical compsns. containing them. WO 0002860.

HuEP5C7

285630

ACTION – Humanized monoclonal antibody that simultaneously blocks E- and P-selectin without complement fixation. When compound (20 mg/kg i.v.) was administered immediately after the onset of ischemia in baboons subjected to 1-h occlusion of the anterior cerebral arteries and the left internal cerebral artery, a significant reduction in the number of major strokes and mean stroke volume, as well as an improvement in neurological deficits, was seen; immunohistochemical analysis also indicated a reduction in neutrophil infiltration into ischemic brain tissue. No immunosuppression was observed. Potentially useful for the treatment of stroke.

SOURCE – Protein Design Labs.

REFERENCES

1. Choudhri, T.F. et al. Simultaneous E- and P-selectin blockade improves outcome in a double-blinded, placebo-controlled study of primate stroke. Stroke 2000, 31(1): Abst P220.

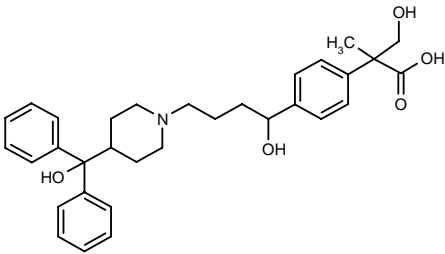
2. He, X.-Y. et al. Humanization and pharmacokinetics of a monoclonal antibody with specificity for both E- and P-selectin. J Immunol 1998, 160(2): 1029.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

285201

3-Hydroxy-2-[4-[1-hydroxy-4-[4-(1-hydroxy-1,1-diphenylmethyl)piperidin-1-yl]butyl]phenyl]-2-methylpropionic acid



C32 H39 N O5; Mol wt: 517.6621

ACTION – Antiallergic agent, a histamine H₁ receptor antagonist (K_i = 0.36 μM for inhibition of [³H]-pyrilamine binding in rat cortex preparations).

SOURCE – Aventis Pharma.

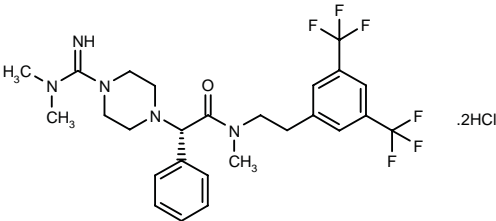
REFERENCES

1. Ayers, T.A. and Brown, P.W. (Aventis Pharmaceuticals Inc.) Novel antihistaminic piperidine derivs. and intermediates for the preparation thereof. WO 0001671.

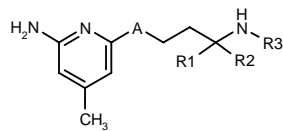
ASTHMA THERAPY

284220

N-[2-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-2(S)-[4-(N,N-dimethylamidino)piperazin-1-yl]-N-methyl-2-phenylacetamide dihydrochloride



C26 H31 F6 N5 O . 2HCl; Mol wt: 616.4747



Compound	R1	R2	R3	A	Formula
285325	H	H	2,5-(OH)2-3-i-Pr-PhCO	-CH2-	C ₂₀ H ₂₇ N ₃ O ₃
285326	-O-		4-N(Me)2-Ph	-(CH2)3-	C ₂₀ H ₂₉ ClN ₄ O
285327	-O-		4-N(Me)2-Ph	-(CH2)2-	C ₁₉ H ₂₇ ClN ₄ O
285328	H	H	3-MeO-4-OH-PhCH=CHCH2	-CH2-	C ₂₀ H ₂₈ ClN ₃ O ₂
285330	H	H	2-OH-4,5-(MeO)2-PhCH2	-CH2-	C ₁₉ H ₂₇ N ₃ O ₃

SOURCE – SCRAS.

REFERENCES

1. Chabrier de Lassauniere, P.-E. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) 2-Aminopyridine derivs., their use as medicines and pharmaceutical compsns. containing them. WO 0002860.

HuEP5C7

285630

ACTION – Humanized monoclonal antibody that simultaneously blocks E- and P-selectin without complement fixation. When compound (20 mg/kg i.v.) was administered immediately after the onset of ischemia in baboons subjected to 1-h occlusion of the anterior cerebral arteries and the left internal cerebral artery, a significant reduction in the number of major strokes and mean stroke volume, as well as an improvement in neurological deficits, was seen; immunohistochemical analysis also indicated a reduction in neutrophil infiltration into ischemic brain tissue. No immunosuppression was observed. Potentially useful for the treatment of stroke.

SOURCE – Protein Design Labs.

REFERENCES

1. Choudhri, T.F. et al. Simultaneous E- and P-selectin blockade improves outcome in a double-blinded, placebo-controlled study of primate stroke. Stroke 2000, 31(1): Abst P220.

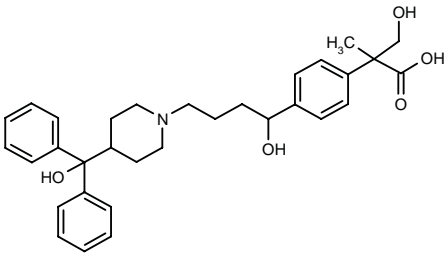
2. He, X.-Y. et al. Humanization and pharmacokinetics of a monoclonal antibody with specificity for both E- and P-selectin. J Immunol 1998, 160(2): 1029.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

285201

3-Hydroxy-2-[4-[1-hydroxy-4-[4-(1-hydroxy-1,1-diphenylmethyl)piperidin-1-yl]butyl]phenyl]-2-methylpropionic acid



C32 H39 N O5; Mol wt: 517.6621

ACTION – Antiallergic agent, a histamine H₁ receptor antagonist (K_i = 0.36 μM for inhibition of [³H]-pyrilamine binding in rat cortex preparations).

SOURCE – Aventis Pharma.

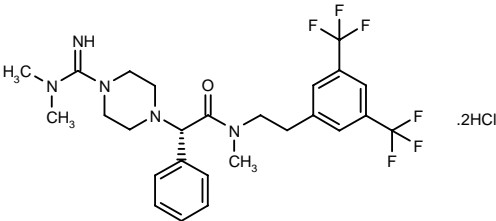
REFERENCES

1. Ayers, T.A. and Brown, P.W. (Aventis Pharmaceuticals Inc.) Novel antihistaminic piperidine derivs. and intermediates for the preparation thereof. WO 0001671.

ASTHMA THERAPY

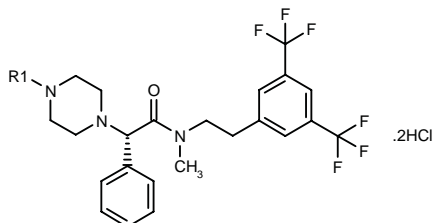
284220

N-[2-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-2(S)-[4-(N,N-dimethylamidino)piperazin-1-yl]-N-methyl-2-phenylacetamide dihydrochloride



C26 H31 F6 N5 O . 2HCl; Mol wt: 616.4747

ACTION – Tachykinin antagonist active against substance P, but also against neurokinin A and neurokinin B, proven to inhibit [125 I]-substance P binding to cloned NK₁ receptors in human lymphoblastoma IM-9 cells with an IC₅₀ value of 0.12 nM. Potentially useful for the treatment or prevention of neurokinin-mediated diseases such as asthma, bronchitis, rhinitis, conjunctivitis, dermatitis, urticaria, arthritis, irritable colon, ulcerative colitis, vomiting, pain and migraine. A representative compound from a series of guanidine and amidine derivatives, wherein the following are also included:



Compound	R1	Formula
284221	1-Me-4,5-dihydro-2-imidazolyl	C ₂₇ H ₃₁ F ₈ N ₅ O ₂ ·2HCl
284222	C(=NMe)NHMe	C ₂₆ H ₃₁ F ₈ N ₅ O ₂ ·2HCl
284223	4-morpholinyl-C(=NH)	C ₂₈ H ₃₃ F ₆ N ₅ O ₂ ·2HCl
284224	i-PrNHC(=NH)	C ₂₇ H ₃₃ F ₈ N ₅ O ₂ ·2HCl

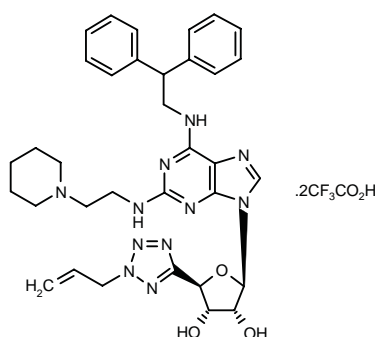
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Esser, F. et al. (Boehringer Ingelheim Pharma KG) *Novel neurokinin antagonists, methods for the production thereof and pharmaceutical compns. containing said cpds.* DE 19824470, WO 9962893.

284943

2(*R*)-[2-(2-Allyl-2*H*-tetrazol-5-yl)-5(*R*)-[6-(2,2-diphenylethylamino)-2-[2-(1-piperidinyl)ethylamino]-9*H*-purin-9-yl]tetrahydrofuran-3(*S*),4(*R*)-diol bis(trifluoroacetate)



C34 H41 N11 O3 . 2 C2 H F3 O2; Mol wt: 879.8157

ACTION – Antiinflammatory agent that inhibits leukocyte recruitment and activation and acts as a selective adenosine A_{2A} receptor agonist; it is therefore expected to have an improved profile over known nonselective adenosine A_{2A} agonists. Selectivity was demonstrated by EC₅₀ values, expressed as a ratio of that of the nonselective agent NECA, of 26.38, > 6131 and > 165 for A_{2A}, A₃ and A₁ receptors, respectively. Potentially useful in inflammatory diseases in which leukocytes are implicated, particularly asthma and chronic obstructive pulmonary disease (COPD). A representative compound from a series of 2-(purin-9-yl)tetrahydrofuran-3,4-diol derivatives.

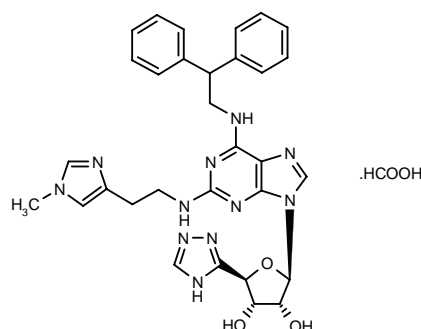
SOURCE – Glaxo Wellcome.

REFERENCES

1. Allen, D.G. et al. (Glaxo Group Ltd.) *2-(Purin-9-yl)-tetrahydrofuran-3,4-diol derivs.* WO 9967265.

284945

2(*R*)-[6-(2,2-Diphenylethylamino)-2-[2-(1-methyl-1*H*-imidazol-4-yl)ethylamino]-9*H*-purin-9-yl]-5(*R*)-(4*H*-1,2,4-triazol-3-yl)tetrahydrofuran-3(*R*),4(*S*)-diol formate



C31 H33 N11 O3 . C H2 O2; Mol wt: 653.7005

ACTION – Antiinflammatory agent that inhibits leukocyte recruitment and activation and acts as a selective adenosine A_{2A} receptor agonist; it is therefore expected to have an improved profile over known nonselective adenosine A_{2A} agonists. Selectivity was demonstrated by EC₅₀ values, expressed as a ratio of that of the nonselective agent NECA, of 1.08, > 430 and 1003.4 for A_{2A}, A₃ and A₁ receptors, respectively. Potentially useful in inflammatory diseases in which leukocytes are implicated, particularly asthma and chronic obstructive pulmonary disease (COPD). A representative compound from a series of 2-(purin-9-yl)tetrahydrofuran-3,4-diol derivatives.

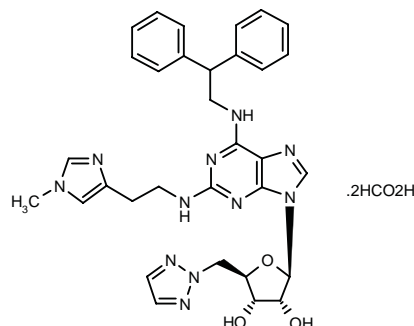
SOURCE – Glaxo Wellcome.

REFERENCES

1. Allen, D.G. et al. (Glaxo Group Ltd.) *2-(Purin-9-yl)-tetrahydrofuran-3,4-diol derivs.* WO 9967263.

284946

2(*R*)-[6-(2,2-Diphenylethylamino)-2-[2-(1-methyl-1*H*-imidazol-4-yl)ethylamino]-9*H*-purin-9-yl]-5(*R*)-(2*H*-1,2,3-triazol-2-ylmethyl)tetrahydrofuran-3(*R*),4(*S*)-diol diformate



C32 H35 N11 O3 . 2 C H2 O2; Mol wt: 713.7521

ACTION – Antiinflammatory agent that inhibits leukocyte recruitment and activation and acts as a selective adenosine A_{2A} receptor agonist; it is therefore expected to have an improved profile over known nonselective adenosine A_{2A} agonists. Selectivity was demonstrated by EC₅₀ values, expressed as a ratio of that of the nonselective agent NECA, of 1.31, > 147 and 3038.8, respectively, for A_{2A}, A₃ and A₁ receptors. Potentially useful in inflammatory diseases in which leukocytes are implicated, particularly asthma and chronic obstructive pulmonary disease (COPD). A representative compound from a series of 2-(purin-9-yl)tetrahydrofuran-3,4-diol derivatives.

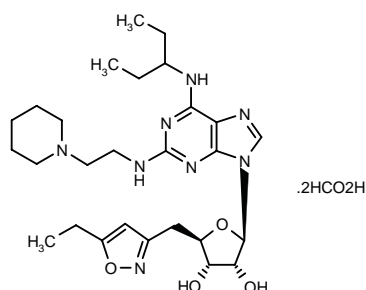
SOURCE – Glaxo Wellcome.

REFERENCES

1. Allen, D.G. et al. (Glaxo Group Ltd.) 2-(Purin-9-yl)-tetrahydrofuran-3,4-diol derivs. WO 9967266.

284947

2-(R)-(5-Ethylisoxazol-3-ylmethyl)-5(R)-[6-(1-ethyl-propylamino)-2-[2-(1-piperidinyl)ethylamino]-9H-purin-9-yl]tetrahydrofuran-3(S),4(R)-diol diformate



C₂₇ H₄₂ N₈ O₄ · 2 C H₂ O₂; Mol wt: 634.7304

ACTION – Antiinflammatory agent that inhibits leukocyte recruitment and activation and acts as a selective adenosine A_{2A} receptor agonist; it is therefore expected to have an improved profile over known nonselective adenosine A_{2A} agonists. Selectivity was demonstrated by EC₅₀ values, expressed as a ratio of that of the nonselective agent NECA, of 3.25, > 1124 and 21.82, respectively, for A_{2A}, A₃ and A₁ receptors. Potentially useful in inflammatory diseases in which leukocytes are implicated, particularly asthma and chronic obstructive pulmonary disease (COPD). A specifically claimed compound from a series of 2-(purin-9-yl)tetrahydrofuran-3,4-diol derivatives.

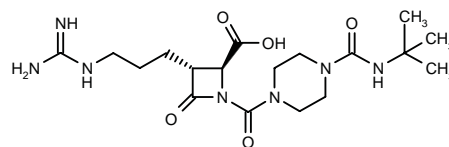
SOURCE – Glaxo Wellcome.

REFERENCES

1. Allen, D.G. et al. (Glaxo Group Ltd.) 2-(Purin-9-yl)-tetrahydrofuran-3,4-diol derivs. WO 9967264.

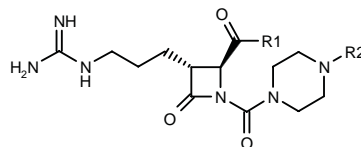
284969

3(R)-(3-Guanidinopropyl)-1-[4-[N-(tert-butyl)carbamoyl]-piperazin-1-ylcarbonyl]-4-oxoazetidine-2(S)-carboxylic acid



C₁₈ H₃₁ N₇ O₅; Mol wt: 425.4869

ACTION – Tryptase inhibitor with potential as an antiinflammatory agent, particularly in the treatment of chronic asthma, as well as allergic rhinitis, inflammatory bowel disease, psoriasis, conjunctivitis, atopic dermatitis, rheumatoid arthritis, osteoarthritis and other chronic inflammatory joint diseases or diseases of joint cartilage destruction. Other specifically claimed compounds from this series of amidino and guanidino azetidinone derivatives include the following:



Compound	R1	R2	Formula
284971	OH	1,4,5,6-tetrahydro-2-pyrimidinyl	C ₁₇ H ₂₈ N ₈ O ₄
284972	4-(NH ₂ CO)-1-Pip	CO ₂ CH(i-Pr) ₂	C ₂₇ H ₄₆ N ₈ O ₆
284974	1-Piz	CO ₂ CH(i-Pr) ₂	C ₂₅ H ₄₄ N ₈ O ₅
284975	4-(NH ₂ CO)-1-Piz	1,4,5,6-tetrahydro-2-pyrimidinyl	C ₂₂ H ₃₇ N ₁₁ O ₄
284976	OH	CONH(CH ₂) ₅ Ph	C ₂₅ H ₃₇ N ₇ O ₅

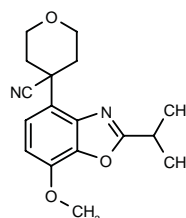
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Bisacchi, G. et al. (Bristol-Myers Squibb Co.) Amidino and guanidino azetidinone tryptase inhibitors. WO 9967215.

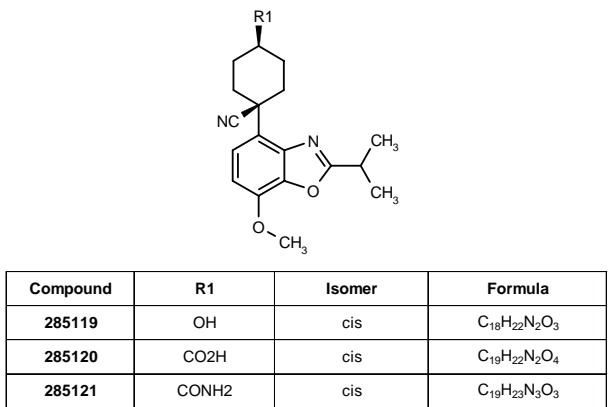
285118

4-(2-Isopropyl-7-methoxybenzoxazol-4-yl)tetrahydropyran-4-carbonitrile



C₁₇ H₂₀ N₂ O₃; Mol wt: 300.3560

ACTION – Bronchodilating and antiinflammatory agent, particularly useful for the treatment of respiratory disorders, an inhibitor of phosphodiesterase type 4 (PDE4; -log IC₅₀ = 7.86); it is reported to possess low toxicity and high bioavailability. Within this series of benzoxazole derivatives, the following are also included:



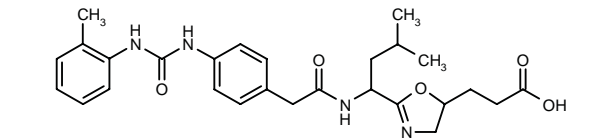
SOURCE – Byk Gulden.

REFERENCES

1. Ulrich, W.-R. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *New benzoxazoles with PDE-inhibiting activity*. WO 0001695.

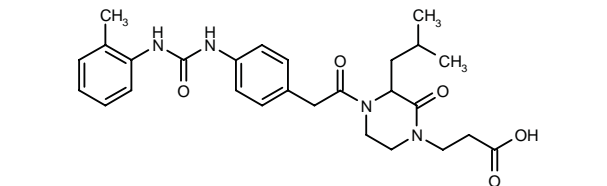
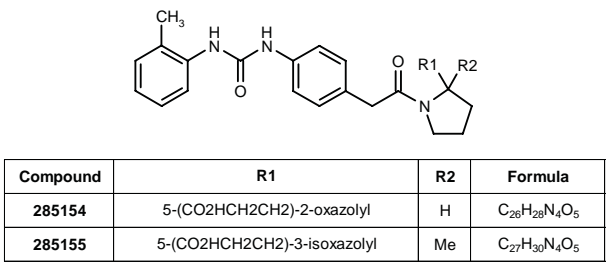
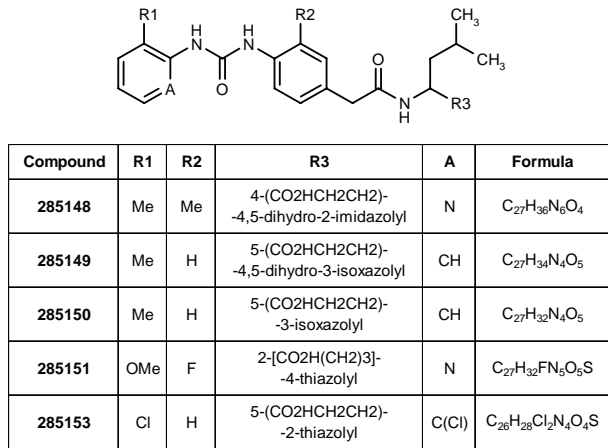
285147

3-[2-[3-Methyl-1-[2-[4-[3-(2-methylphenyl)ureido]phenyl]-acetamido]butyl]-4,5-dihydrooxazol-5-yl]propionic acid



C₂₇ H₃₄ N₄ O₅; Mol wt: 494.5886

ACTION – Agent for the treatment of inflammatory, auto-immune or respiratory disorders such as asthma, multiple sclerosis, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, psoriasis, organ transplant rejection and atherosclerosis, a potent inhibitor of VLA-4 (α₄β₁, CD49d/CD29) binding to proteins such as vascular cell adhesion molecule-1 (VCAM-1), the HepII/IIICS domain (CS-1 region) of fibronectin and osteopontin. Other specifically claimed compounds from this series of nonpeptide inhibitors include the following:



285152: C₂₇ H₃₄ N₄ O₅

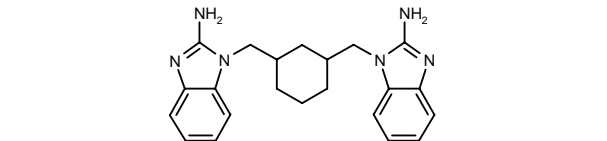
SOURCE – Pfizer.

REFERENCES

1. Duplantier, A.J. et al. (Pfizer Products Inc.) *Non-peptidyl inhibitors of VLA-4 dependent cell binding useful in treating inflammatory, autoimmune, and respiratory diseases*. WO 0000477.

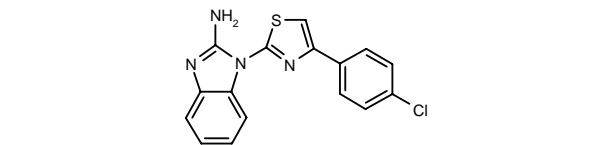
285170

1,1'-(Cyclohexane-1,3-diyl)bis(methylene)bis(1H-benzimidazol-2-amine)

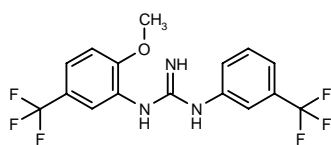
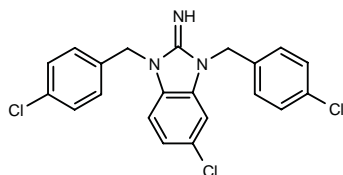
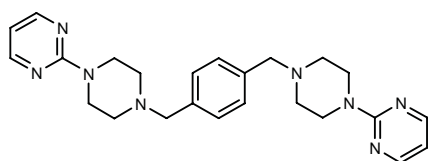
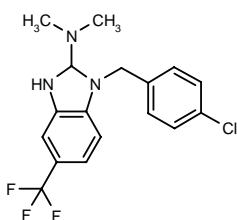
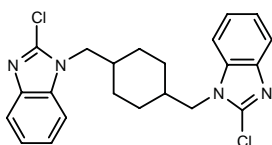
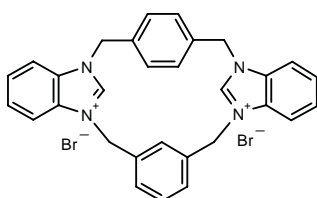


C₂₂ H₂₆ N₆; Mol wt: 374.4894

ACTION – A selective small-conductance Ca²⁺-sensitive potassium SK channel blocker with potential in the treatment or prevention of a broad range of conditions including asthma, cystic fibrosis, chronic obstructive pulmonary disease, convulsions, vascular and coronary artery spasms, renal diseases, urinary incontinence, irritable bowel syndrome, gastrointestinal dysfunction, cerebral and cardiac ischemia, angina pectoris, coronary heart disease, traumatic brain injury, psychosis, anxiety, depression, dementia, Alzheimer's disease, dysmenorrhea, Raynaud's disease, migraine, arrhythmia, hypertension, type II diabetes, hyperinsulinemia, premature labor, baldness, cancer and immune suppression. Other specifically claimed compounds include the following:



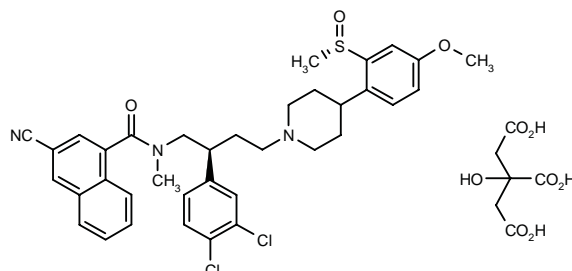
285172: C₁₆ H₁₁ Cl N₄ S

**285174:** C₁₆ H₁₃ F₆ N₃ O**285176:** C₂₁ H₁₆ Cl₃ N₃**285178:** C₂₄ H₃₀ N₈**285180:** C₁₇ H₁₇ Cl F₃ N₃**285182:** C₂₂ H₂₂ Cl₂ N₄**285183:** C₃₀ H₂₆ Br₂ N₄*SOURCE* – NeuroSearch.**REFERENCES**

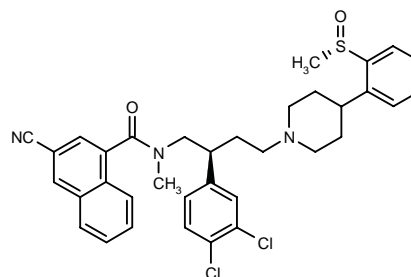
1. Teuber, L. et al. (NeuroSearch A/S) *Potassium channel blocking agents*. WO 0001676.

285317

3-Cyano-*N*-[2-(*S*)-(3,4-dichlorophenyl)-4-[4-[4-methoxy-2-[(*S*)-methylsulfinyl]phenyl]piperidin-1-yl]butyl]-*N*-methylnaphthalene-1-carboxamide citrate

C₃₆ H₃₇ Cl₂ N₃ O₃ S . C₆ H₈ O₇; Mol wt: 854.8005

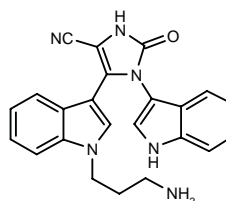
ACTION – Neurokinin receptor antagonist acting at NK₁ and NK₂ receptors, as demonstrated in functional assays by pK_B values of 8.1 and 8.7 for NK₁ and NK₂ receptors, respectively. *In vivo*, compound was shown to inhibit NK₁ and NK₂ receptor-mediated bronchoconstriction in guinea pigs. Potentially useful for the treatment of asthma, chronic obstructive pulmonary disease, inflammation, pain, depression, anxiety and urinary incontinence. Another specifically claimed compound is:

**285318:** C₃₅ H₃₅ Cl₂ N₃ O₂ S*SOURCE* – AstraZeneca.**REFERENCES**

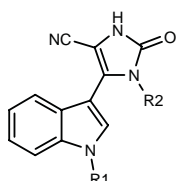
1. Bernstein, P.R. et al. (Zeneca Ltd.) *N*-Substd. naphthalene carboxamides as neurokinin-receptor antagonists. WO 0002859.

285338

5-[1-(3-Aminopropyl)-1*H*-indol-3-yl]-1-(1*H*-indol-3-yl)-2-oxo-2,3-dihydro-1*H*-imidazole-4-carbonitrile

C₂₃ H₂₀ N₆ O; Mol wt: 396.4520

ACTION – Protein kinase C (PKC) inhibitor potentially useful in the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or neurodegenerative disorders, preferably in the oral or topical treatment of inflammatory airways disorders such as asthma or bronchitis, atopic diseases such as rhinitis or atopic dermatitis, inflammatory bowel diseases such as Crohn's disease or colitis, autoimmune diseases such as multiple sclerosis, diabetes, atherosclerosis, psoriasis, systemic lupus erythematosus or rheumatoid arthritis, malignant diseases, HIV infection or AIDS and for inhibiting organ transplant rejection. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
285339	(CH ₂) ₃ NH ₂	1-Me-3-indolyl	C ₂₄ H ₂₂ N ₆ O
285340	(CH ₂) ₄ NH ₂	3-NO ₂ -Ph	C ₂₂ H ₂₀ N ₆ O ₃
285341	4-MeO-PhCH ₂	1-Me-3-indolyl	C ₂₉ H ₂₃ N ₅ O ₂
285342	(CH ₂) ₃ Br	1-Me-3-indolyl	C ₂₄ H ₂₀ BrN ₅ O
285343	cis-4-NH ₂ -cyclohexyl	1-Me-3-indolyl	C ₂₇ H ₂₆ N ₆ O

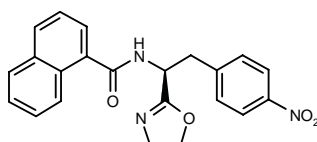
SOURCE – AstraZeneca.

REFERENCES

1. Karabelas, K. et al. (Astra AB) *New pharmaceutically active cpds.* WO 0002877.

285389

N-[1-(*S*)-(4,5-Dihydrooxazol-2-yl)-2-(4-nitrophenyl)ethyl]-naphthalene-1-carboxamide



C₂₂ H₁₉ N₃ O₄; Mol wt: 389.4091

ACTION – Chemokine CCR3 receptor antagonist (IC₅₀ = 0.56 μM against [¹²⁵I]-eotaxin binding in human eosinophils) with potential in the treatment of allergic disorders including bronchial asthma, conjunctivitis, allergic rhinitis, nasal polyposis, atopic dermatitis, eczema, pruritus and inflammatory bowel disease.

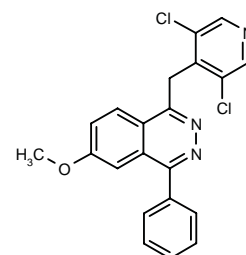
SOURCE – SmithKline Beecham.

REFERENCES

1. Dhanak, D. (SmithKline Beecham Corp.) *CCR-3 receptor antagonists.* WO 0004003.

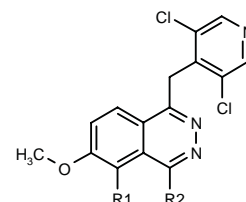
285699

1-(3,5-Dichloropyridin-4-ylmethyl)-6-methoxy-4-phenyl-phthalazine

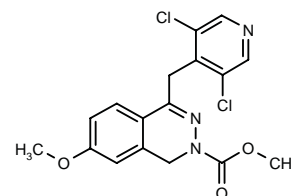


C₂₁ H₁₅ Cl₂ N₃ O; Mol wt: 396.2755

ACTION – Agent for the treatment of allergic and inflammatory disorders, particularly respiratory disorders, a selective phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 37 ± 6 nM versus 7 and 21% inhibition of PDE3 and PDE5, respectively, at 1 μM). In addition, compound inhibited lipopolysaccharide-stimulated TNF-α release from human monocytes with an IC₅₀ of 46 ± 15 nM. Other specifically claimed compounds from this series of phthalazine derivatives include the following:



Compound	R1	R2	Formula
285702	ethynylene-CH ₂ N(Me)CH ₂ Ph	H	C ₂₆ H ₂₂ Cl ₂ N ₄ O
285703	4-morpholinyl-(CH ₂) ₃ -ethynylene	H	C ₂₄ H ₂₆ Cl ₂ N ₄ O ₂
285704	ethynylene-CH ₂ OH	H	C ₁₈ H ₁₃ Cl ₂ N ₃ O ₂
285705	H	4-morpholinyl	C ₁₉ H ₁₈ Cl ₂ N ₄ O ₂
285706	H	1,2,4-triazol-1-yl	C ₁₇ H ₁₂ Cl ₂ N ₆ O



285700: C₁₇ H₁₅ Cl₂ N₃ O₃

SOURCE – Zambon.

REFERENCES

1. Napoletano, M. et al. (Zambon Group SpA) *Phthalazine derivs. phosphodiesterase 4 inhibitors.* WO 0005218.

ALPROGEN

284921

Single glycoprotein component isolated from crude aloe extract with a molecular weight of approximately 10 kDa and an isoelectric point of 6.0

ACTION – Antiallergic agent, a single component of crude aloe extract that significantly and concentration-dependently (1-5 µg/ml) decreases histamine and leukotriene release and completely blocks Ca²⁺ influx in antigen-activated guinea pig lung mast cells; it was also able to concentration-dependently decrease protein kinase C (PKC) and phospholipase D activities and inhibit 1,2-diacylglycerol (DAG) formation and phospholipase A₂ (PLA₂) activity during mast cell activation.

SOURCES – Korea University, Seoul (KR); Namyang Aloe; Seoul National University, Seoul (KR); Yonsei University, Seoul (KR).

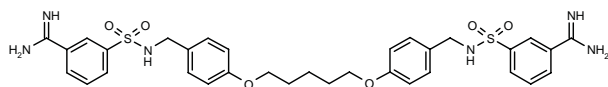
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AMG-126737*

276928

N,N'-(Pentane-1,5-diyl)bis(oxy)bis(1,4-phenylene)bis-(methylene)bis(3-amidinobenzenesulfonamide)



C33 H38 N6 O6 S2; Mol wt: 678.8312

ACTION – Antiasthmatic agent, a potent and selective inhibitor of human mast cell tryptase (K_i = 90 nM) with > 10-200-fold selectivity over other trypsin-like serine proteases including plasmin, trypsin, factor Xa and plasma kallikrein (K_i = 930, 2500, 6400 and 18,000 nM, respectively) and no activity against thrombin, cathepsin G, chymotrypsin or elastase at up to 100 µM. In antigen-challenged guinea pigs, compound inhibited the development of airways hyperresponsiveness when given intratracheally (ED₅₀ = 0.015 mg/kg), orally (10 mg/kg) or i.p. (10 mg/kg) at 1 h before antigen. In a sheep model of allergen-induced airways responses, it was shown to inhibit both early- and late-phase bronchoconstriction (77 and 92% inhibition, respectively, at 3 mg by aerosol b.i.d. for 3 days) and the development of airways hyper-responsiveness to carbachol at 24 h following antigen challenge.

SOURCES – Amgen; Array BioPharma.

REFERENCES

1. Burgess, L. and Rizzi, J.P. (Array BioPharma, Inc.) *Cpds. which inhibit tryptase activity.* WO 9924395.

2. Burgess, L.E. et al. *Potent selective nonpeptidic inhibitors of human lung tryptase.* Proc Natl Acad Sci USA 1999, 96(15): 8348.

3. Wright, C.D. et al. *Inhibition of allergen-induced pulmonary responses by the selective tryptase inhibitor 1,5-bis-(4-[(3-carbamimidoyl-benzenesulfonylamino)-methyl]phenoxy)-pentane (AMG-126737).* Biochem Pharmacol 1999, 58(12): 1989.

*Identified compound **276928** (see **276927**) Drug Data Rep 1999, 021(07): 0594.

MET-CHEMOKINE β SEVEN

285302

Modified form of the β-chemokine macrophage inflammatory protein MIP-4, also known as pulmonary and activation-regulated chemokine (PARC), alternative macrophage activation-associated C-C chemokine (AMAC-1) or dendritic cell-derived C-C chemokine (DCCK-1)

Met-CkB7

ACTION – Chemokine CCR3 receptor antagonist, a modified form of the β-chemokine MIP-4 (macrophage inflammatory protein 4) that is able to prevent eotaxin-, MCP-4- or cotaxin-2-induced Ca²⁺ flux into HOS-CCR3 cells at a concentration of about 25 nM and to completely block eotaxin- or MCP-4-induced Ca²⁺ flux into eosinophils at concentrations of 50 and 10 nM, respectively. Compound was more potent than Met- and aminooxypentane (AOP)-RANTES as a CCR3 antagonist and, unlike Met- or AOP-RANTES, it was devoid of partial agonist activity and was highly specific for this receptor. Binding studies showed that it was more effective in displacing [¹²⁵I]-eotaxin binding in transfected HOS-CCR3 cells, with an IC₅₀ of 6 nM versus respective values of 10 and 50 nM for eotaxin and MCP-4; both compound (IC₅₀ = 5 nM) and eotaxin (IC₅₀ = 5 nM) were more effective than MCP-4 (IC₅₀ = 25 nM) in displacing [¹²⁵I]-MCP-4 binding. In addition compound was able to inhibit eotaxin- and MCP-4-induced eosinophil chemotaxis at concentrations as low as 1 nM. Potentially useful for the treatment of diseases characterized by inappropriate influx and activation of leukocytes within tissues such as allergies, asthma, chronic inflammatory diseases and autoimmune diseases.

SOURCES – CRC Beatson Laboratories; Human Genome Sciences.

REFERENCES

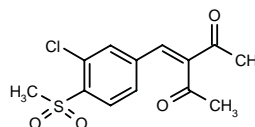
1. Nibbs, R.J.B. et al. *C-C chemokine receptor 3 antagonism by the β-chemokine macrophage inflammatory protein 4, a property strongly enhanced by an amino-terminal alanine-methionine swap.* J Immunol 2000, 164(1): 1488.

2. *Human Genome Sciences moves three drugs into clinical development in 1999.* DailyDrugNews.com (Daily Essentials) 2000, Feb 24.

OR-1958

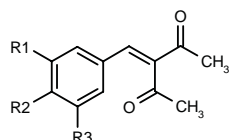
285099

3-[3-Chloro-4-(methylsulfonyl)benzylidene]pentane-2,4-dione



C13 H13 Cl O4 S; Mol wt: 300.7607

ACTION – Agent for the treatment and prevention of respiratory disorders such as asthma, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), allergic rhinitis and related inflammatory conditions that is reported to act in the same way as the corticosteroid budesonide; however, because it acts locally and decomposes in the blood circulation, it is reported to be particularly well suited for the treatment of asthma in patients who cannot use steroid therapy. Compound was shown to reduce PAF-induced airways eosinophilia in guinea pig lung in a dose-dependent manner when administered as an infusion into the airways. Moreover, compound did not induce local irritation in a number of guinea pig and rabbit models, contrary to the structurally related agent OR-1364. Other specifically claimed compounds from this series of substituted β -diketones include the following:



Compound	R1	R2	R3	Formula
285100	H	SO ₂ Me	F	C ₁₃ H ₁₃ FO ₄ S
285101	H	SO ₂ Me	Br	C ₁₃ H ₁₃ BrO ₄ S
285102	Cl	SO ₂ Me	Cl	C ₁₃ H ₁₂ Cl ₂ O ₄ S
285103	SO ₂ Me	Cl	H	C ₁₃ H ₁₃ ClO ₄ S

SOURCE – Orion Corporation.

REFERENCES

1. Aho, P. et al. (Orion Corporation) *Subst. β -diketones and their use*. WO 0001667.

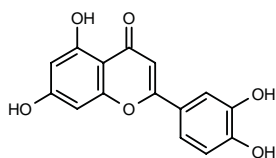
TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES (COPD)

LUTEOLIN

244028

2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one

3',4',5,7-Tetrahydroxyflavone



C₁₅H₁₀O₆; Mol wt: 286.2380

ACTION – Antiinflammatory agent, a natural plant extract used in Chinese medicine for the treatment of bronchitis. In animals, compound showed marked inhibitory activity on acute inflammatory responses such as carrageenan-induced rat paw edema (ED₅₀ = 106 mg/kg i.m.), croton oil-induced air pouch granuloma in rats, carrageenan- or yeast-induced ankle joint swelling in rats and acetic acid-induced pleurisy in rats. *In vitro*, at concentrations of 0.4-

10 μ M it reduced H₂O₂ release from peritoneal macrophages stimulated by opsonized zymosan. Compound showed *in vitro* spasmolytic activity in pre-contracted guinea pig ileum (IC₅₀ = 27.6 μ M) and electrically stimulated rat vas deferens (IC₅₀ = 43.4 μ M), and it was able to inhibit histamine release from guinea pig lungs. Immunoregulatory activity was seen in experimental animals with suppressed immune function and in patients with bronchitis. Compound showed antitussive, expectorant and slight antibacterial effects with little toxicity and few side effects. In preliminary clinical studies in chronic bronchitis patients, compound induced complete remission in 63% of patients and was effective in reducing major symptoms including cough, asthma, sputum and whistling, with no liver, cardiac or renal toxicity. Potentially useful for the treatment of chronic bronchitis.

SOURCES – Chinese Academy of Medical Sciences, Beijing (CN); Institute of Materia Medica, Beijing (CN).

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- Huang, Y. et al. *Effects of luteolin and quercetin, inhibitors of tyrosine kinase, on cell growth and metastasis-associated properties in A431 cells overexpressing epidermal growth factor receptor*. Br J Pharmacol 1999, 128(5): 999.
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- Lu, Y.H. et al. *Synthesis of luteolin and kaempferol*. Acta Pharm Sin 1980, 15(8): 477.
- Ma, J.Y. et al. *Studies on chemical constituents of Ixeris denticulata f. pinnatifida*. J Chin Pharm Univ 1998, 29: 167.
- Park, K.Y. et al. *Inhibitory effect of luteolin 4'-O-glucoside from Kummerowia striata and other flavonoids on interleukin-5 bioactivity*. Planta Med 1999, 65(5): 457.
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- Zheng, Y.W. et al. *Effect of luteolin on H₂O₂ release of peritoneal macrophages in rats*. Chin Pharmacol Bull 1990, 6: 56.

MONOGRAPH – Wang, X.-W. *Luteolin*. Drugs Fut 2000, 25(2): 0146.

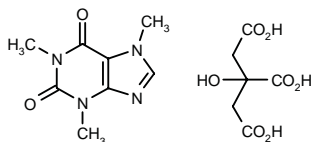
AGENTS FOR RESPIRATORY DISTRESS SYNDROME

CAFFEINE CITRATE

285181

1,3,7-Trimethyl-3,7-dihydro-1H-purine-2,6-dione citrate

1,3,7-Trimethylxanthine citrate



C₈ H₁₀ N₄ O₂ · C₆ H₈ O₇; Mol wt: 386.3152

ACTION – CNS stimulant, cardiac muscle and bronchial smooth muscle relaxant and diuretic whose effects are attributed to antagonism of both adenosine A₁ and A₂ receptors.

INDICATION – Short-term treatment of apnea of prematurity in infants between 28 and < 33 weeks' gestational age.

PRESENTATION – Single-dose vial containing 3 ml of solution, 20 mg/ml equivalent to 10 mg/ml caffeine base.

PROPRIETARY NAME – *Cafcit* (US).

SOURCES – Ben Venue; Roxane.

REFERENCES

- Amato, M. et al. *Percutaneous caffeine application in the treatment of neonatal apnea*. Eur J Pediatr 1991, 150(8): 592.
- Anwar, M. et al. *Effect of caffeine on pneumogram and apnea of infancy*. Arch Dis Child 1986, 61(9): 891.
- Aranda, J.V. et al. *Efficacy of caffeine in treatment of apnea in the low birth weight infant*. J Pediatr 1977, 90(3): 467.
- Autret, E. et al. *Comparison of 2 different maintenance doses of caffeine in the treatment of apnea in premature infants*. Therapie 1985, 40(4): 235.
- Dager, S.R. et al. *Human brain metabolic response to caffeine and the effects of tolerance*. Am J Psychiatry 1999, 156(2): 229.
- Erenberg, A. et al. *Results of the first double blind placebo (PL) controlled study of caffeine citrate (CC) for the treatment of apnea of prematurity (AOP)*. J Invest Med 1998, 46(1): 157A.
- Erenberg, A. et al. *Results of the first double blind placebo (PL) controlled study of caffeine citrate (CC) for the treatment of apnea of prematurity (AOP)*. Pediatrics 1998, 102(3, Part 2): 756.
- Erenberg, A. et al. *Results of the first double blind placebo (PL) controlled study of caffeine citrate (CC) for the treatment of apnea of prematurity (AOP)*. Pediatr Res 1998, 43(4, Part 2): 172A.
- Larsen, P.B. et al. *Aminophylline versus caffeine citrate for apnea and bradycardia prophylaxis in premature neonates*. Acta Paediatr 1995, 84(4): 360.
- Lee, T.C. et al. *Population pharmacokinetics of intravenous caffeine in neonates with apnea of prematurity*. Clin Pharmacol Ther 1997, 61(6): 628.
- Lee, T.C. et al. *Saliva as a valid alternative to serum in monitoring intravenous caffeine treatment for apnea of prematurity*. Ther Drug Monit 1996, 18(3): 288.
- Leff, R. et al. *Caffeine pharmacokinetics (PK) in premature infants with apnea of prematurity (AOP)*. J Invest Med 1998, 46(1): 137A.
- Marks, K.H. et al. *The metabolic effects of caffeine citrate in premature infants with apnea*. Pediatr Res 1980, 14(4, Part 2): 605.

14. Romagnoli, C. et al. *Effectiveness and side effects of two different doses of caffeine in preventing apnea in premature infants*. Ther Drug Monit 1992, 14(1): 14.

15. Subhani, M.T. et al. *Pre-discharge event recording in infants with resolving apnea of prematurity (AOP) treated with caffeine citrate*. Pediatr Res 1999, 45(4, Part 2): 756.

16. *Roxane launches orphan drug for treatment of apnea in premature infants*. DailyDrugNews.com (Daily Essentials) 2000, Feb 3.

INOMax®

284439

Gaseous blend of nitric oxide (0.8%) and nitrogen (99.2%) for inhalation

ACTION – Pulmonary vasodilator.

INDICATION – Treatment of hypoxic respiratory failure in term or near-term infants in conjunction with ventilatory support and other appropriate agents.

PRESENTATION – Portable aluminum cylinders containing 353 l at STP of nitric oxide gas (under high pressure of 2000 pounds per square inch gauge [psig]) in 800 ppm concentration in nitrogen (delivered volume: 344 l); 353 l at STP of NO gas in 100 ppm concentration in nitrogen (delivered volume: 344 l); 1963 l at STP of NO gas in 800 ppm concentration in nitrogen (delivered volume: 1918 l); and 1963 l at STP of NO gas in 100 ppm concentration in nitrogen (delivered volume: 1918 l).

PROPRIETARY NAME – *INOMax* (US).

SOURCE – INO Therapeutics.

REFERENCES

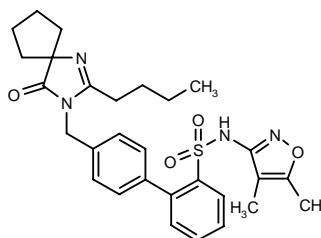
- Clark, R.H. et al. *Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn*. New Engl J Med 2000, 342(7): 469.
- FDA approves new treatment for respiratory failure in neonates. DailyDrugNews.com (Daily Essentials) 1999, Dec 30.
- First market introduction for *INOMax*. DailyDrugNews.com (Daily Essentials) 2000, Feb 15.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

285279

4'-(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-ylmethyl)-N-(4,5-dimethylisoxazol-3-yl)biphenyl-2-sulfonamide



C₂₉ H₃₄ N₄ O₄ S; Mol wt: 534.6776

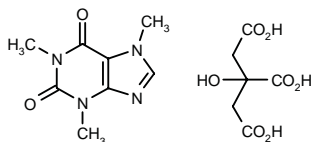
AGENTS FOR RESPIRATORY DISTRESS SYNDROME

CAFFEINE CITRATE

285181

1,3,7-Trimethyl-3,7-dihydro-1H-purine-2,6-dione citrate

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ACTION – CNS stimulant, cardiac muscle and bronchial smooth muscle relaxant and diuretic whose effects are attributed to antagonism of both adenosine A₁ and A₂ receptors.

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PROPRIETARY NAME – *Cafcit* (US).

SOURCES – Ben Venue; Roxane.

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3. Aranda, J.V. et al. *Efficacy of caffeine in treatment of apnea in the low birth weight infant*. J Pediatr 1977, 90(3): 467.
4. Autret, E. et al. *Comparison of 2 different maintenance doses of caffeine in the treatment of apnea in premature infants*. Therapie 1985, 40(4): 235.
5. Dager, S.R. et al. *Human brain metabolic response to caffeine and the effects of tolerance*. Am J Psychiatry 1999, 156(2): 229.
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7. Erenberg, A. et al. *Results of the first double blind placebo (PL) controlled study of caffeine citrate (CC) for the treatment of apnea of prematurity (AOP)*. Pediatrics 1998, 102(3, Part 2): 756.
8. Erenberg, A. et al. *Results of the first double blind placebo (PL) controlled study of caffeine citrate (CC) for the treatment of apnea of prematurity (AOP)*. Pediatr Res 1998, 43(4, Part 2): 172A.
9. Larsen, P.B. et al. *Aminophylline versus caffeine citrate for apnea and bradycardia prophylaxis in premature neonates*. Acta Paediatr 1995, 84(4): 360.
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11. Lee, T.C. et al. *Saliva as a valid alternative to serum in monitoring intravenous caffeine treatment for apnea of prematurity*. Ther Drug Monit 1996, 18(3): 288.
12. Leff, R. et al. *Caffeine pharmacokinetics (PK) in premature infants with apnea of prematurity (AOP)*. J Invest Med 1998, 46(1): 137A.
13. Marks, K.H. et al. *The metabolic effects of caffeine citrate in premature infants with apnea*. Pediatr Res 1980, 14(4, Part 2): 605.

14. Romagnoli, C. et al. *Effectiveness and side effects of two different doses of caffeine in preventing apnea in premature infants*. Ther Drug Monit 1992, 14(1): 14.

15. Subhani, M.T. et al. *Pre-discharge event recording in infants with resolving apnea of prematurity (AOP) treated with caffeine citrate*. Pediatr Res 1999, 45(4, Part 2): 756.

16. *Roxane launches orphan drug for treatment of apnea in premature infants*. DailyDrugNews.com (Daily Essentials) 2000, Feb 3.

INOMax[®]

284439

Gaseous blend of nitric oxide (0.8%) and nitrogen (99.2%) for inhalation

ACTION – Pulmonary vasodilator.

INDICATION – Treatment of hypoxic respiratory failure in term or near-term infants in conjunction with ventilatory support and other appropriate agents.

PRESENTATION – Portable aluminum cylinders containing 353 l at STP of nitric oxide gas (under high pressure of 2000 pounds per square inch gauge [psig]) in 800 ppm concentration in nitrogen (delivered volume: 344 l); 353 l at STP of NO gas in 100 ppm concentration in nitrogen (delivered volume: 344 l); 1963 l at STP of NO gas in 800 ppm concentration in nitrogen (delivered volume: 1918 l); and 1963 l at STP of NO gas in 100 ppm concentration in nitrogen (delivered volume: 1918 l).

PROPRIETARY NAME – *INOMax* (US).

SOURCE – INO Therapeutics.

REFERENCES

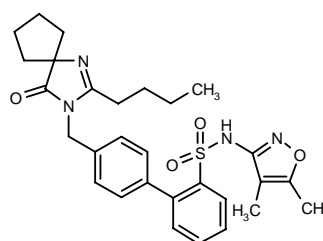
1. Clark, R.H. et al. *Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn*. New Engl J Med 2000, 342(7): 469.
2. *FDA approves new treatment for respiratory failure in neonates*. DailyDrugNews.com (Daily Essentials) 1999, Dec 30.
3. *First market introduction for INOMax*. DailyDrugNews.com (Daily Essentials) 2000, Feb 15.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

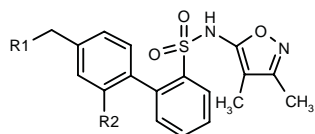
285279

4'-(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-ylmethyl)-N-(4,5-dimethylisoxazol-3-yl)biphenyl-2-sulfonamide

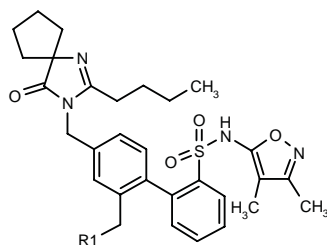


C₂₉ H₃₄ N₄ O₄ S; Mol wt: 534.6776

ACTION – Dual angiotensin and endothelin receptor antagonist with potential in the treatment of hypertension, pulmonary hypertension, sexual dysfunction, heart failure, atherosclerosis, restenosis, endotoxemia, cancer, migraine, asthma, ischemia, subarachnoid hemorrhage, benign prostatic hypertrophy and renal failure. Other specifically claimed compounds within this series of biphenyl sulfonamides include the following:



Compound	R1	R2	Formula
285280	2-Pr-4-Cl-5-[N(Me)2CO]-1-imidazolyl	H	C ₂₇ H ₃₀ ClN ₅ O ₄ S
285282	-N(COC5H11)-L-Ile-NHMe	H	C ₃₁ H ₄₂ N ₄ O ₅ S
285286	3-MeO-2,6-(Me)2-4-Pyr-O	CH ₂ CH ₂ CF ₃	C ₃₁ H ₃₃ F ₃ N ₄ O ₆ S



Compound	R1	Formula
285281	1-Me-2-pyrrolyl-CON(Me)	C ₃₇ H ₄₄ N ₆ O ₅ S
285283	1-pyrazolyl	C ₃₃ H ₃₈ N ₆ O ₄ S
285284	CH ₂ CH ₂ CF ₃	C ₃₂ H ₃₇ F ₃ N ₄ O ₄ S

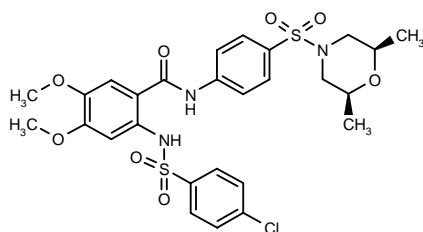
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Murugesan, N. et al. (Bristol-Myers Squibb Co.) *Biphenyl sulfonamides as dual angiotensin endothelin receptor antagonists*. WO 0001389.

285316

2-(4-Chlorophenylsulfonamido)-N-[4-(*cis*-2,6-dimethyl-morpholin-4-ylsulfonyl)phenyl]-4,5-dimethoxybenzamide



C₂₇ H₃₀ Cl N₃ O₈ S₂; Mol wt: 624.1320

ACTION – Potent guanylate cyclase activator with potential in the treatment and prophylaxis of disorders associated with low cGMP levels including cardiovascular disorders such as hypertension, angina pectoris, cardiac insufficiency, thrombosis and atherosclerosis. Compound was shown to produce 24.4-fold stimulation of soluble guanylate cyclase from bovine lung at a concentration of 50 μ M. In addition, it was shown to relax phenylephrine-precontracted rat aortic rings both with and without endothelium (IC₅₀ = 0.67 and 0.29 μ M, respectively). When tested *in vivo* in anesthetized pigs, it caused significant reductions in systolic and diastolic blood pressure, left ventricular end-diastolic pressure (LVEDP), dP/dt_{max} and heart rate, with a duration of action over 180 min at a dose of 10 mg/kg i.d. A representative compound from a series of sulfur substituted sulfonylaminocarboxylic acid *N*-arylamides.

SOURCE – Aventis Pharma.

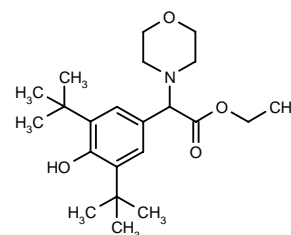
REFERENCES

1. Schindler, U. et al. (Aventis Pharma Deutschland GmbH) *Sulfur subst. sulfonylaminocarboxylic acid N-arylamides, their preparation, their use and pharmaceutical preparations comprising them*. DE 19830430, WO 0002851.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

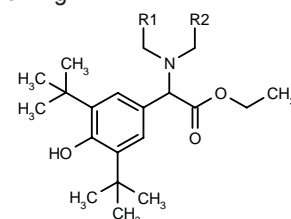
285345

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-(4-morpholinyl)-acetic acid ethyl ester



C₂₂ H₃₅ N₄ O₄; Mol wt: 377.5215

ACTION – Agent for the treatment of atherosclerosis, coronary heart disease and restenosis, an inhibitor of lipoprotein(a) (Lp[a]) production, as demonstrated by IC₅₀ values of 0.8 and 1.3 μ M in the Lp(a) biochemical coupling (LPABC) and LPA3 assays, respectively. Other compounds from this series of phenyl glycine derivatives include the following:



Compound	R1	R2	Formula
285346	3-Pyr	3-Pyr	C ₃₀ H ₃₉ N ₃ O ₃
285347	cyclohexyl	3-Pyr	C ₃₁ H ₄₆ N ₂ O ₃
285348	-(CH ₂) ₂ -		C ₂₂ H ₃₅ N ₃ O ₃

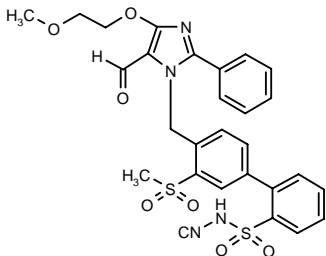
SOURCE – Warner-Lambert.

REFERENCES

1. Lee, H.T. et al. (Warner-Lambert Co.) *Phenyl glycine cpds. and method of treating atherosclerosis and restenosis*. US 6017918.

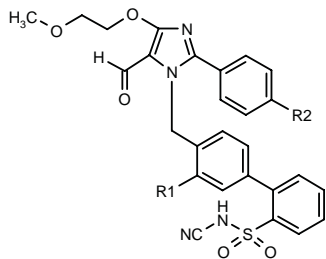
285468

N-Cyano-4'-[5-formyl-4-(2-methoxyethoxy)-2-phenyl-1H-imidazol-1-ylmethyl]-3'-(methylsulfonyl)biphenyl-2-sulfonamide



C28 H26 N4 O7 S2; Mol wt: 594.6664

ACTION – An inhibitor of Na⁺-dependent Cl⁻/HCO₃⁻ exchange (NCBE), as demonstrated in human endothelial cells (about 90.2% inhibition at a concentration of 10 μM), with cardioprotective and antiproliferative activity. Potentially useful for the treatment or prevention of ischemic disorders, myocardial infarction, angina pectoris, stroke, shock states, respiratory disorders and proliferative disorders. Other compounds from this series of N-cyanosulfamoylbiphenylmethylimidazoles include the following:



Compound	R1	R2	Formula
285469	Cl	H	C ₂₇ H ₂₃ ClN ₄ O ₅ S
285470	H	i-Pr	C ₃₀ H ₃₀ N ₄ O ₅ S
285471	OCH ₂ CH ₂ OMe	H	C ₃₀ H ₃₀ N ₄ O ₇ S

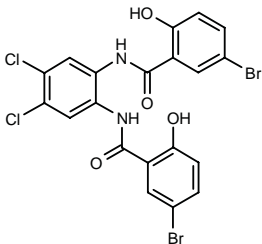
SOURCE – Aventis Pharma.

REFERENCES

1. Kleemann, H.-W. et al. (Aventis Pharma Deutschland GmbH) *Imidazole derivs. with biphenylsulfonyl substitution, method for preparing them and their use as a drug or diagnostic agent*. DE 19832428, WO 0003996.

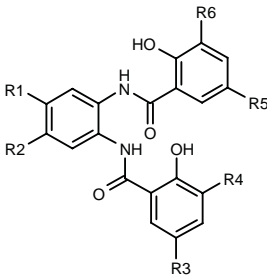
285677

N,N'-Bis(5-bromo-2-hydroxybenzoyl)-4,5-dichlorophenylene-1,2-diamine



C20 H12 Br2 Cl2 N2 O4; Mol wt: 575.0388

ACTION – Macrophage scavenger receptor (MSR) antagonist that inhibits lipid accumulation within macrophage-derived foam cells, with potential in the treatment of cardiovascular disorders such as atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia due to clotting, stroke, myocardial infarction, organ transplant, organ failure and hypercholesterolemia. Other specifically claimed compounds from this series of phenylenediamine derivatives include the following:



Compound	R1=R2	R3=R5	R4=R6	Formula
285678	H	Br	H	C ₂₀ H ₁₄ Br ₂ N ₂ O ₄
285680	H	CF ₃	H	C ₂₂ H ₁₄ F ₆ N ₂ O ₄
285681	Cl	CF ₃	H	C ₂₂ H ₁₂ Cl ₂ F ₆ N ₂ O ₄
285683	Cl	H	Ph	C ₃₂ H ₂₂ Cl ₂ N ₂ O ₄
285744	H	H	Ph	C ₃₂ H ₂₄ N ₂ O ₄

SOURCE – SmithKline Beecham.

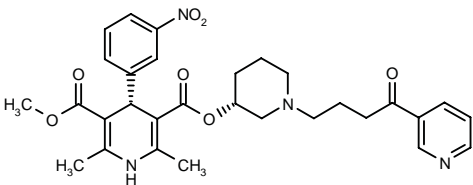
REFERENCES

1. Weinstock, J. and Franz, R.G. (SmithKline Beecham Corp.) *Macrophage scavenger receptor antagonists*. WO 0003704.

CRL-42482

285464

2,6-Dimethyl-4(S)-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl 5-[1-[4-oxo-4-(pyridin-3-yl)-butyl]piperidin-3(R)-yl] diester



C30 H34 N4 O7; Mol wt: 562.6196

ACTION – Antianginal agent, a calcium antagonist with high affinity for the dihydropyridine binding site in rat ventricular membranes (IC_{50} = 28 nM) and proven to potently antagonize KCl-induced contractions of isolated rat aorta (IC_{50} = 140 nM). In anesthetized dogs, it increased coronary flow starting at doses of 20 µg/kg i.v., while showing a minimal arrhythmogenic dose of 1280 µg/kg i.v., thus exhibiting a therapeutic margin of 64.

SOURCE – Lafon.

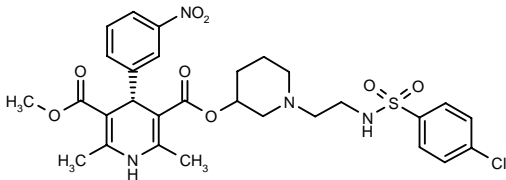
REFERENCES

1. Personnier, A. et al. (Laboratoires L. Lafon) 1-4-Dihydropyridines with pyridinyl group as calcium blockers. FR 2781225, WO 0003712.

CRL-42635

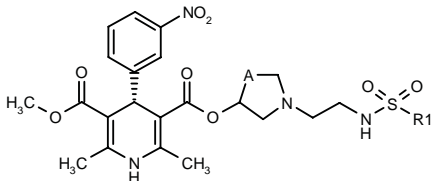
285402

2,6-Dimethyl-4(S)-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[1-[2-(4-chlorophenylsulfonamido)-ethyl]piperidin-3-yl] 5-methyl diester



C29 H33 Cl N4 O8 S; Mol wt: 633.1187

ACTION – Calcium antagonist particularly useful for the treatment of stable angina by virtue of its ability to improve myocardial oxygen supply by increasing coronary flow, and to reduce myocardial oxygen consumption by decreasing contractility. Compound was shown to bind to the dihydropyridine (DHP) site in rat cardiac ventricle homogenates with an IC_{50} of 8.7 nM and inhibited KCl-induced contractions of rat aorta with an IC_{50} of 360 nM. Compound also gave a minimal effective dose for increasing coronary flow in dogs of 40 µg/kg i.v. versus a minimal arrhythmogenic dose of 1280 µg/kg i.v. (therapeutic index = 32). A representative compound from a series of 1,4-dihydropyridine derivatives, wherein the following are also included:



Compound	R1	A	Isomer	Formula
CRL-42517 [285403]	Ph	-(CH2)2-	R	C ₂₉ H ₃₄ N ₄ O ₈ S
CRL-42600 [285404]	Ph	-CH2-		C ₂₈ H ₃₂ N ₄ O ₈ S
CRL-42658 [285405]	CH2Ph	-(CH2)2-		C ₃₀ H ₃₆ N ₄ O ₈ S

SOURCE – Lafon.

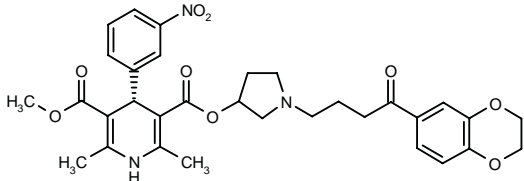
REFERENCES

1. Personnier, A. et al. (Laboratoires L. Lafon) 1,4-Dihydropyridines as calcium blockers. FR 2781224, WO 0003987.

CRL-42962

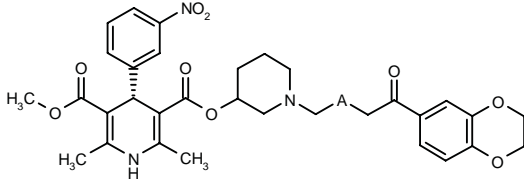
285397

2,6-Dimethyl-4(S)-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[1-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-oxobutyl]pyrrolidin-3-yl] 5-methyl diester



C32 H35 N3 O9; Mol wt: 605.6405

ACTION – Calcium antagonist particularly useful for the treatment of stable angina by virtue of its ability to improve myocardial oxygen supply by increasing coronary flow, and to reduce myocardial oxygen consumption by decreasing contractility. Compound was shown to inhibit KCl-induced rat aorta contractions with an IC_{50} of 400 nM and gave a minimal effective dose for increasing coronary flow in dogs of 10 µg/kg i.v. versus a minimal arrhythmogenic dose of 1280 µg/kg i.v. (therapeutic index = 128). Other specifically claimed compounds from this series of 1,4-dihydropyridine derivatives with a benzodioxocarbonyl substituent include the following:



Compound	A	Isomer	Formula
CRL-42925 [285398]	-CH2-	R	C ₃₃ H ₃₇ N ₃ O ₉
CRL-42943 [285399]	-CH2-	S	C ₃₃ H ₃₇ N ₃ O ₉
CRL-42979 [285400]	-(CH2)2-		C ₃₄ H ₃₉ N ₃ O ₉

SOURCE – Lafon.

REFERENCES

1. Personnier, A. et al. (Laboratoires L. Lafon) 1-4-Dihydropyridines with benzodioxo carbonyl group as calcium blockers. FR 2781226, WO 0004015.

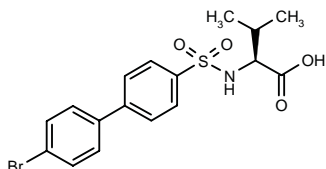
HEART FAILURE THERAPY

PD-166793*

259040

N-(4'-Bromobiphenyl-4-ylsulfonyl)-L-valine

PD-166793-0000



C17 H18 Br N O4 S; Mol wt: 412.3022

ACTION – Matrix metalloproteinase (MMP) inhibitor with selectivity for MMP-2 (gelatinase A; $IC_{50} = 4$ nM), MMP-3 (stromelysin; $IC_{50} = 7$ nM) and MMP-13 (collagenase 3; $IC_{50} = 8$ nM) over MMP-1 (fibroblast collagenase; $IC_{50} = 6$ μ M), MMP-7 (matrilysin; $IC_{50} = 7.2$ μ M) and MMP-9 (gelatinase B; $IC_{50} = 7.9$ μ M) and inactive (at 100 μ M) against a number of other enzymes and receptors. Compound exhibited a good oral pharmacokinetic profile in three rats, dogs and monkeys following chronic dosing at 3 mg/kg/day p.o. for 2 weeks. In a model of myocardial infarction in rats where MMP-2 expression was consistently elevated 2-3-fold compared to sham-operated animals, compound at doses of 0.005-5 mg/kg/day for 6 weeks starting at 2 weeks postmyocardial infarction significantly reduced MMP-2 levels, reduced left ventricular dilatation and improved systolic function. Synergistic beneficial effects have also been seen in combination with an angiotensin-converting enzyme (ACE) inhibitor in spontaneously hypertensive heart failure rats and the paced pig model of heart failure. Potentially useful for the treatment of pathological processes related to overproduction of MMPs including rheumatoid arthritis and osteoarthritis, tumor growth and metastasis, abdominal aortic aneurysms and progressive cardiac dilatation in patients with congestive heart failure.

SOURCE – Warner-Lambert.

REFERENCES

1. Bocan, T.M.A. et al. (Warner-Lambert Co.) *Use of matrix metalloproteinase inhibitors for treating neurological disorders and promoting wound healing*. WO 9826773.
2. Newton, R.S. and Roth, B.D. (Warner-Lambert Co.) *Statin-matrix metalloproteinase inhibitor combinations*. WO 9947138.
3. O'Brien, P.M. and Sliskovic, D.R. (Warner-Lambert Co.) *Biphenylsulfonamide matrix metalloproteinase inhibitors*. EP 0901466, WO 9744315.
4. Peterson, J.T. Jr. (Warner-Lambert Co.) *Method for treating and preventing heart failure and ventricular dilatation*. WO 9825597.
5. Peterson, J.T. Jr. and Pressler, M.L. (Warner-Lambert Co.) *ACE inhibitor-MMP inhibitor combinations*. WO 9932150.
6. Hua, L. et al. *MMP upregulation in the myocardial infarcted rat and the effect of MMP-inhibitor treatment with PD 166793*. Circulation 1998, 98(17, Suppl.): Abst 2198.
7. Li, H. et al. *Effect of PD166793 & quinapril on MMP & TIMP expression during the development of heart failure in the SHHF rat*. J Mol Cell Cardiol 1998, 30(7): Abst 88.
8. Mcelmurray, J.H. III et al. *Angiotensin-converting enzyme and matrix metalloproteinase inhibition with developing heart failure: Comparative effects on left ventricular function and geometry*. J Pharmacol Exp Ther 1999, 291(2): 799.

9. O'Brien, P.M. et al. *Structure-activity relationships and pharmacokinetic analysis for a series of potent, systemically available biphenylsulfonamide matrix metalloproteinase inhibitors*. J Med Chem 2000, 43(2): 156.

10. Parker, M.H. et al. *Analysis of the binding of hydroxamic acid and carboxylic acid inhibitors to the stromelysin-1 (matrix metalloproteinase-3) catalytic domain by isothermal titration calorimetry*. Biochemistry 1999, 38(41): 13592.

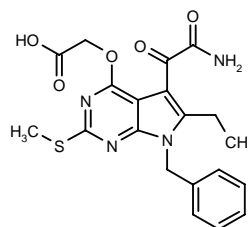
11. Peterson, T. et al. *Matrix metalloproteinase inhibitor, PD 166793, alters progression of heart failure in the myocardial infarcted rat*. Circulation 1998, 98(17, Suppl.): Abst 2200.

*Identified compound **259040** Drug Data Rep 1998, 020(03): 0257.

TREATMENT OF SHOCK

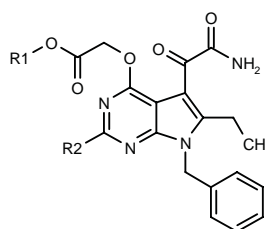
285024

2-[5-(2-Amino-2-oxoacetyl)-7-benzyl-6-ethyl-2-(methylsulfanyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]acetic acid



C20 H20 N4 O5 S; Mol wt: 428.4670

ACTION – Agent for the treatment of septic shock, inflammatory bowel disease, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis, rheumatoid arthritis and osteoarthritis, an inhibitor of secretory phospholipase A_2 (sPLA₂; $IC_{50} = 0.019$ μ M against recombinant human enzyme). Within this series of pyrrolo[2,3-d]pyrimidine derivatives, the following are also specifically claimed:



Compound	R1	R2	Formula
285025	Me	Me	C ₂₁ H ₂₂ N ₄ O ₅
285027	Me	H	C ₂₀ H ₂₀ N ₄ O ₅
285028	H	Me	C ₂₀ H ₂₀ N ₄ O ₅
285029	H	H	C ₁₉ H ₁₈ N ₄ O ₅

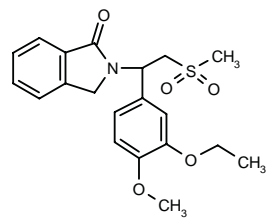
SOURCE – Lilly.

REFERENCES

1. Hutchison, D.R. et al. (Eli Lilly and Company) *Bicyclic sPLA₂ inhibitors*. WO 0000201.

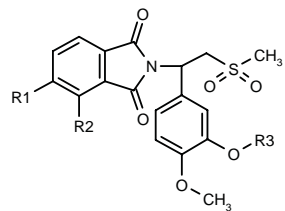
285511

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)-ethyl]-2,3-dihydro-1*H*-isindol-1-one

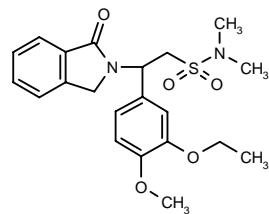


C20 H23 N O5 S; Mol wt: 389.4697

ACTION – Agent for the treatment of inflammatory, immune, infectious and malignant conditions such as septic shock, postischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, AIDS, rheumatoid arthritis, osteoarthritis, Crohn’s disease, ulcerative colitis, multiple sclerosis and systemic lupus erythematosus that acts by reducing TNF- α and NF κ B levels and by inhibiting phosphodiesterases, particularly PDE4. Other specifically claimed compounds within this series of substituted phenethylsulfones include the following:



Compound	R1	R2	R3	Formula
285513	H	H	Et	C ₂₀ H ₂₁ NO ₆ S
285514	NO ₂	H	Et	C ₂₀ H ₂₀ N ₂ O ₆ S
285515	H	NO ₂	Et	C ₂₀ H ₂₀ N ₂ O ₆ S
285516	H	NH ₂	Et	C ₂₀ H ₂₂ N ₂ O ₆ S
285517	Me	H	Et	C ₂₁ H ₂₃ NO ₆ S
285518	NHAc	H	Et	C ₂₂ H ₂₄ N ₂ O ₇ S
285519	H	N(Me) ₂	Et	C ₂₂ H ₂₆ N ₂ O ₆ S
285520	N(Me) ₂	H	Et	C ₂₂ H ₂₆ N ₂ O ₆ S
285521	-CH=CHCH=CH-		Et	C ₂₄ H ₂₃ NO ₆ S
285522	H	OMe	Et	C ₂₁ H ₂₃ NO ₇ S
285523	H	H	cyclopentyl	C ₂₃ H ₂₅ NO ₆ S
285524	H	N(Me) ₂	cyclopentyl	C ₂₅ H ₃₀ N ₂ O ₆ S



285512: C21 H26 N2 O5 S

SOURCE – Celgene.

REFERENCES

1. Muller, G.W. and Man, H.-W. (Celgene Corp.) *Substd. phenethylsulfones and method of reducing TNF α levels*. US 6020358.

ISIS-27616

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is: GCCCAAACTCTGTTGAA

284608

ACTION – Antisense phosphorothioate oligodeoxynucleotide that specifically hybridizes with nucleic acids encoding human cytosolic phospholipase A₂ (cPLA₂) and modulates its expression. It was shown to inhibit cPLA₂ mRNA levels by 100% at a concentration of 150 nM.

SOURCE – Isis Pharmaceuticals.

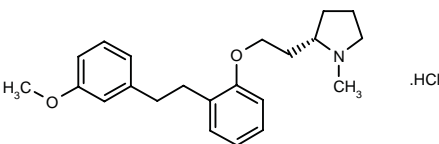
REFERENCES

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TREATMENT OF PERIPHERAL VASCULAR DISEASE

285562

1-Methyl-2(*S*)-[2-[2-[2-(3-methoxyphenyl)ethyl]-phenoxy]ethyl]pyrrolidine hydrochloride



C22 H29 N O2 . HCl; Mol wt: 375.9370

ACTION – Potent 5-HT₂ receptor ligand (IC₅₀ = 1.8 nM) with high selectivity over 5-HT₁ and 5-HT₃ receptors and β -adrenoceptors (IC₅₀ > 5000 nM), dopamine D₂ and α -adrenoceptors (IC₅₀ = 1100 and 490 nM, respectively). Compound exhibited 5-HT₂-antagonist activity, as demonstrated by its ability to inhibit 5-HT-induced vasoconstriction in rat caudal arteries (IC₅₀ = 2.2 nM). Compound was shown to inhibit 5-HT-induced platelet aggregation both *in vitro* (IC₅₀ = 0.057 μ M in human platelet-rich plasma) and *ex vivo* in cats (90% inhibition at 30 min after 100 μ g/kg i.v.). When compared with sarpgregrelate, compound was more potent and selective and demonstrated better efficacy in the inhibition of platelet aggregation both *in vitro* (IC₅₀ < 100 μ M for sarpgregrelate) and *ex vivo*, where the reference compound was not active even at the highest dose of 1000 μ g/kg i.v. Potentially useful for the treatment of peripheral arterial occlusive diseases.

SOURCE – Sankyo.

REFERENCES

1. Fujimoto, K. et al. (Sankyo Co., Ltd.) *Phenoxyalkylamines, -pyrrolidines and -piperidines for the treatment and prevention of circulatory diseases and psychosis*. EP 0600717, JP 1994234736, JP 1994306025, US 5556864.

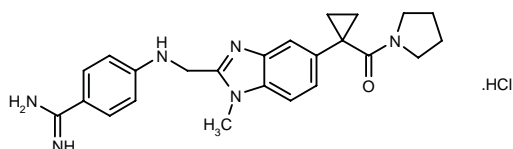
2. Tanaka, N. et al. *[2-(*o*-Phenylalkyl)phenoxy]alkylamines II: Synthesis and selective serotonin-2 receptor binding*. Chem Pharm Bull 2000, 48(2): 245.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

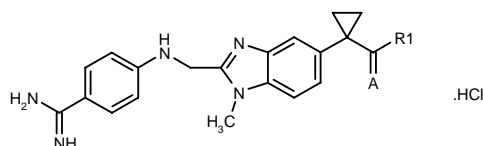
285207

4-[1-Methyl-5-[1-(1-pyrrolidinylcarbonyl)cyclopropyl]-1*H*-benzimidazol-2-ylmethylamino]benzamidinium hydrochloride

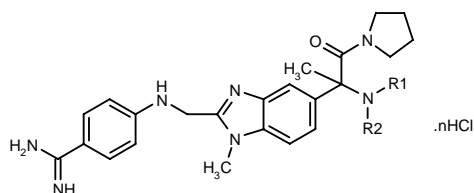


C₂₄H₂₈N₆O . HCl; Mol wt: 452.9871

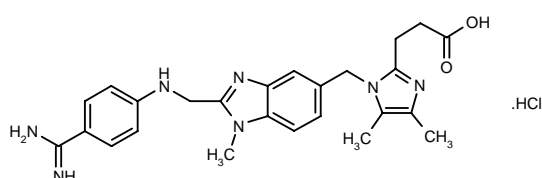
ACTION – Anticoagulant and antithrombotic agent, an inhibitor of serine proteases such as thrombin and/or factor Xa shown to prolong the activated partial thromboplastin time (aPTT) with an ED₂₀₀ value (concentration doubling aPTT) of 0.12 μM. Other specifically claimed compounds within this series of benzimidazole derivatives include the following:



Compound	R1	A	Formula
285208	2-Pyr	-N(OCH ₂ CO ₂ H)-	C ₂₇ H ₂₇ N ₇ O ₃ ·HCl
285210	2-(CH ₂ CH ₂ CO ₂ H)-1-pyrrolidinyl	-O-	C ₂₇ H ₃₂ N ₆ O ₃ ·HCl



Compound	R1	R2	n	Formula
285209	H	CH ₂ CH ₂ CO ₂ H	1	C ₂₆ H ₃₃ N ₇ O ₃ ·HCl
285212	H	CH ₂ CO ₂ H	1	C ₂₅ H ₃₁ N ₇ O ₃ ·HCl
285213	Me	COCH ₂ CO ₂ H	2	C ₂₈ H ₃₅ N ₇ O ₄ ·2HCl



285211: C₂₅H₂₉N₇O₂ . HCl

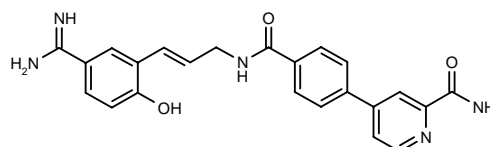
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Ries, U. et al. (Boehringer Ingelheim Pharma KG) *Benzimidazoles, production thereof and use thereof as medicaments*. DE 19829964, WO 0001704.

285750

4-[4-[*N*-[3-(5-Amidino-2-hydroxyphenyl)-2(*E*)-propenyl]carbamoyl]phenyl]pyridine-2-carboxamide



C₂₃H₂₁N₅O₃; Mol wt: 415.4509

ACTION – Anticoagulant, a potent inhibitor of factor Xa ($K_i = 0.75$ nM) with high selectivity relative to other serine proteases including thrombin ($K_i > 4000$ nM), plasmin ($K_i > 7300$ nM), activated protein C ($K_i \sim 18,500$ nM), trypsin ($K_i = 2200$ nM) and tissue plasminogen activator ($K_i = 7700$ nM). It was effective in prolonging the activated partial thromboplastin time (aPTT) in human, dog rabbit and rat plasma, with respective concentrations required to double aPTT of 0.87, 0.99, 0.51 and 1.7 μM.

SOURCE – Aventis Pharma.

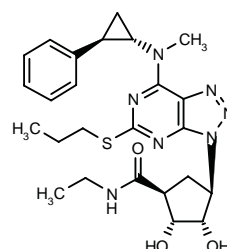
REFERENCES

1. Gong, Y. et al. *Amido-(propyl and allyl)-hydroxybenzamidines: Development of achiral inhibitors of factor Xa*. Bioorg Med Chem Lett 2000, 10(3): 217.

ANTIPLATELET THERAPY

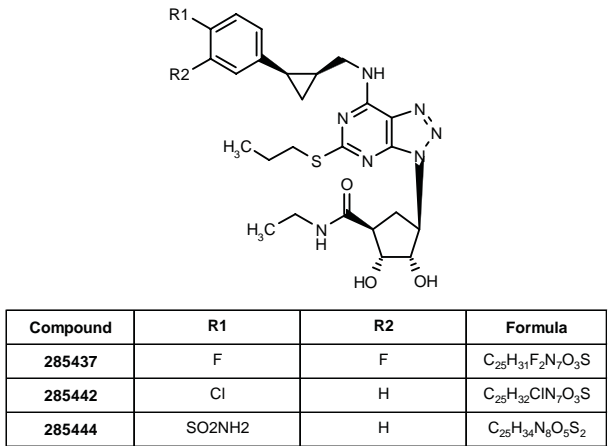
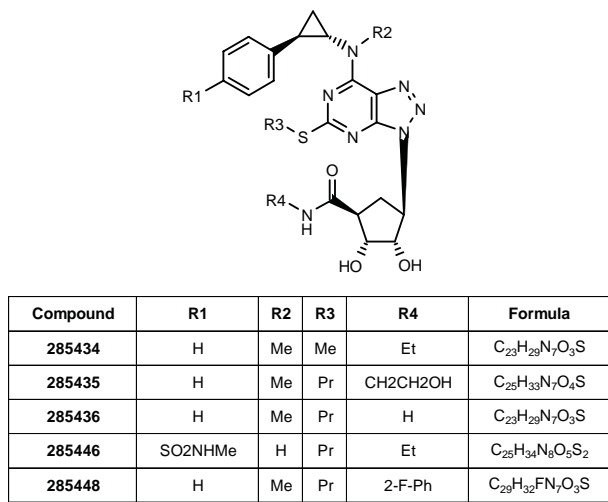
285433

(1*S*,2*R*,3*S*,4*R*)-*N*-Ethyl-2,3-dihydroxy-4-[7-[*N*-methyl-*N*-(1*S*,2*R*)-2-phenylcyclopropyl]amino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-carboxamide



C₂₅H₃₃N₇O₃S; Mol wt: 511.6477

ACTION – Antithrombotic agent with P₂T purinoceptor-antagonist activity, Other specifically claimed compounds from this series of substituted triazolo[4,5-*d*]pyrimidines include the following:



SOURCE – AstraZeneca.

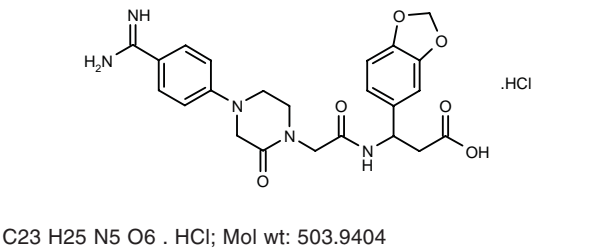
REFERENCES

1. Guile, S. and Springthorpe, B. (Astra Pharmaceuticals Ltd.;Astra AB) *Novel triazolo[4,5-d]pyrimidine cpds.* WO 0004021.

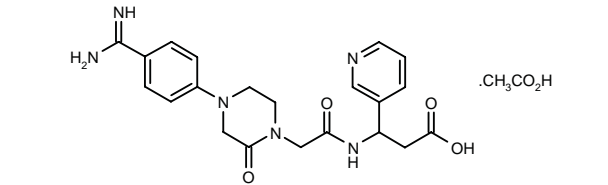
CRL-42788

285472

3-[2-[4-(4-Amidinophenyl)-2-oxopiperazin-1-yl]-acetamido]-3-(1,3-benzodioxol-5-yl)propionic acid hydrochloride



ACTION – Platelet aggregation inhibitor and antithrombotic agent, a fibrinogen (gplIb/IIIa) receptor antagonist proven to inhibit collagen-induced aggregation both *in vitro* in guinea pig and human platelet-rich plasma (PRP; IC₅₀ = 0.15 and 0.34 μM, respectively) and *ex vivo* in guinea pigs (69 and 78% inhibition, respectively, at 1 and 2 h following administration of a dose of 150 mg/kg i.g.). Another piperazinone derivative is:



SOURCE – Lafon.

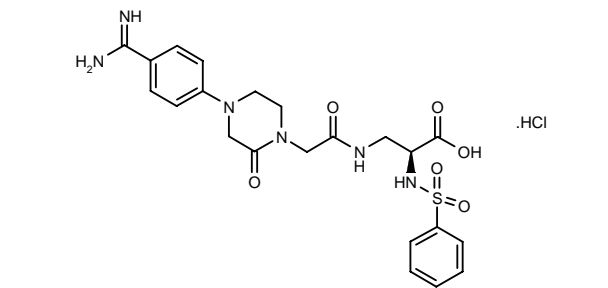
REFERENCES

1. Yue, C. et al. (Laboratoires L. Lafon) *Piperazinone derivs. and their uses.* FR 2781220, WO 0004000.

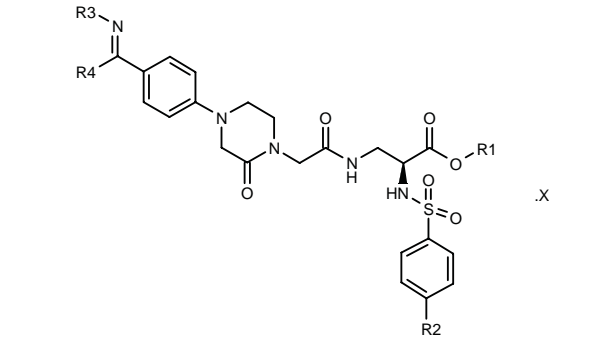
CRL-42872

285492

3-[2-[4-(4-Amidinophenyl)-2-oxopiperazin-1-yl]aceta-mido]-2(S)-(phenylsulfonamido)propionic acid hydrochloride



ACTION – Platelet aggregation inhibitor and antithrombotic agent, a fibrinogen (gplIb/IIIa) receptor antagonist proven to inhibit collagen-induced aggregation both *in vitro* in guinea pig and human platelet-rich plasma (PRP; IC₅₀ = 94 and 120 nM, respectively) and *ex vivo* in guinea pigs (68 and 64% inhibition, respectively, at 1 and 2 h after administration of a dose of 10 mg/kg i.g.). Other specifically claimed compounds from this series of substituted piperazinone derivatives include the following:



Compound	R1	R2	R3	R4	X	Formula
CRL-42817 [285493]	Et	H	H	NH2	acetate	C ₂₄ H ₃₀ N ₆ O ₆ S .C ₂ H ₄ O ₂
285494	H	H	CO ₂ Et	NH2		C ₂₅ H ₃₀ N ₆ O ₈ S
CRL-43100 [285495]	Et	Me	H	4-morpholinyl		C ₂₉ H ₃₈ N ₆ O ₇ S
CRL-42873 [285496]	H	Me	H	NH2	HCl	C ₂₃ H ₂₈ N ₆ O ₆ S .HCl

SOURCE – Lafon.

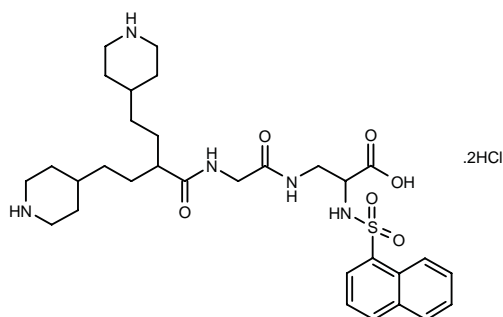
REFERENCES

1. Yue, C. et al. (Laboratoires L. Lafon) *Subst. piperazines and their therapeutic uses*. FR 2781221, WO 0004001.

CRL-42914

285568

2-(1-Naphthylsulfonamido)-3-[2-[4-(4-piperidyl)-2-[2-(4-piperidyl)ethyl]butyramido]acetamido]propionic acid dihydrochloride



C31 H45 N5 O6 S . 2HCl; Mol wt: 688.7133

ACTION – Antithrombotic agent, a fibrinogen (gpIIb/IIIa) receptor antagonist proven to inhibit collagen-induced aggregation both *in vitro* using guinea pig and human platelet-rich plasma (PRP; IC₅₀ = 44 and 580 nM), and *ex vivo* in guinea pigs (81% inhibition at 2 h after administration of 10 mg/kg p.o.). A representative compound from a series of bispiperidines.

SOURCE – Lafon.

REFERENCES

1. Yue, C. et al. (Laboratoires L. Lafon) *Bispiperidines as antithrombotic agents*. FR 2781223, WO 0003986.

MAB 1B5

285629

Hamster monoclonal antibody specific for mouse platelet gpIIb/IIIa (1B5)

ACTION – Hamster monoclonal antibody specific for mouse platelet gpIIb/IIIa, proven to inhibit platelet aggregation in mice and rats without binding to αvβ3 integrin. The F(ab')₂ fragment of the antibody administered to rats prior to the induction of embolic stroke significantly reduced ischemic lesion size and the number of vessels with fibrin deposition, without increasing hemorrhage.

SOURCE – Mount Sinai School of Medicine, New York, NY (US).

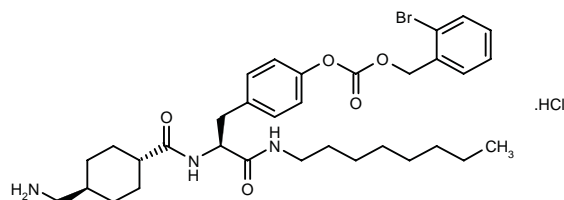
REFERENCES

1. Gang, Z.G. et al. *Beneficial effects of a monoclonal antiplatelet integrin αIIbβ3 antibody treatment of embolic middle cerebral artery occlusion in the rat*. Stroke 2000, 31(1): Abst P219.
2. Lengweiler, S. et al. *Preparation of monoclonal antibodies to murine platelet glycoprotein IIb/IIIa (αIIbβ3) and other proteins from hamster-mouse interspecies hybridomas*. Biochem Biophys Res Commun 1999, 262(1): 167.

HEMOSTATICS

285554

*N*²-[*trans*-4-(Aminomethyl)cyclohexylcarbonyl]-*N*¹-octyl-O-(2-bromobenzoyloxycarbonyl)-L-tyrosinamide hydrochloride



C33 H46 Br N3 O5 . HCl; Mol wt: 681.1073

M.p. 210-2 °C, [α]_D²⁵ +0.7° (c 1.0, MeOH).

ACTION – Potent and selective plasmin inhibitor (IC₅₀ = 0.23 and 0.8 μM, respectively, using S-2251 and fibrin as substrates) with good selectivity over human urokinase and thrombin (IC₅₀ > 25 μM) and plasma kallikrein (IC₅₀ = 16 μM) and moderate activity against trypsin (IC₅₀ = 1.6 μM).

SOURCES – Kobe University, Kobe (JP); Kobe Gakuin University, Kobe (JP).

REFERENCES

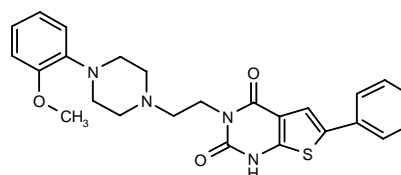
1. Okada, Y. et al. *Development of plasmin selective inhibitors and studies of their structure-activity relationship*. Chem Pharm Bull 2000, 48(2): 184.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

285461

3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-6-phenyl-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-2,4-dione



C25 H26 N4 O3 S; Mol wt: 462.5714

SOURCE – Lafon.

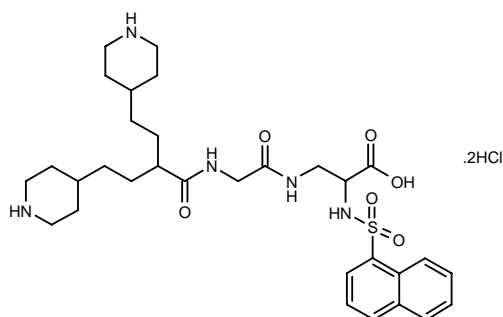
REFERENCES

1. Yue, C. et al. (Laboratoires L. Lafon) *Subst. piperazines and their therapeutic uses*. FR 2781221, WO 0004001.

CRL-42914

285568

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SOURCE – Lafon.

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SOURCE – Mount Sinai School of Medicine, New York, NY (US).

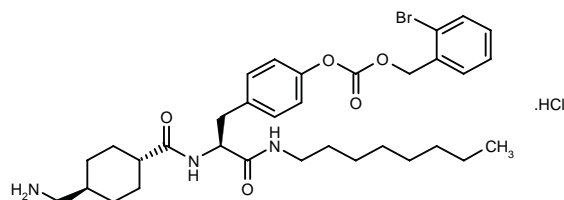
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2. Lengweiler, S. et al. *Preparation of monoclonal antibodies to murine platelet glycoprotein IIb/IIIa (αIIbβ3) and other proteins from hamster-mouse interspecies hybridomas*. Biochem Biophys Res Commun 1999, 262(1): 167.

HEMOSTATICS

285554

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SOURCES – Kobe University, Kobe (JP); Kobe Gakuin University, Kobe (JP).

REFERENCES

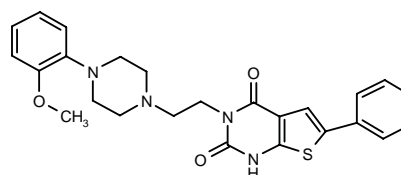
1. Okada, Y. et al. *Development of plasmin selective inhibitors and studies of their structure-activity relationship*. Chem Pharm Bull 2000, 48(2): 184.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

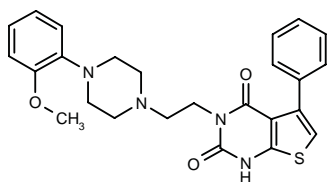
285461

3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-6-phenyl-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-2,4-dione



C25 H26 N4 O3 S; Mol wt: 462.5714

ACTION – Agent for the treatment of benign prostatic hyperplasia (BPH), detrusor instability and incontinence, an α_1 -adrenoceptor antagonist with some degree of selectivity for the α_{1d} subtype (rat; $K_i = 0.361$ nM) over α_{1a} (rat; $K_i = 0.578$ nM) and α_{1b} subtypes (hamster; $K_i = 1.86$ nM). *In vivo*, compound was found to inhibit epinephrine-induced increases in intraurethral pressure in dogs with a pA_2 value of 8.47 versus 6.97 and 8.91 for terazosin and tamsulosin, respectively. Compound exhibited weaker hypotensive properties than terazosin and tamsulosin in a spontaneously hypertensive rat (SHR) model, giving a pED_{50} value of 6.04 versus pED_{50} values of 6.40 and 7.22, respectively, for reference compounds. Another compound from this series of piperazinyl- pyrimidinedione derivatives is:



285462: C₂₅ H₂₆ N₄ O₃ S

SOURCE – Abbott.

REFERENCES

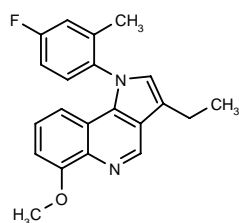
1. Meyer, M.D. and Carroll, W.A. (Abbott Laboratories Inc.) *Piperazinyl pyrimidine dione cpds. selective for adrenoceptors*. WO 0004027.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

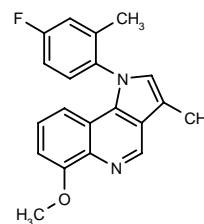
285145

3-Ethyl-1-(4-fluoro-2-methylphenyl)-6-methoxy-1*H*-pyrrolo[3,2-*c*]quinoline



C₂₁ H₁₉ F N₂ O; Mol wt: 334.3921

ACTION – Antiulcer agent that inhibits gastric acid secretion and is reported to exhibit excellent stability. Compound was found to be more potent than omeprazole in inhibiting H^+/K^+ -ATPase *in vitro*, as well as ethanol-induced gastric ulcers in fasted rats following oral administration. No toxicity was observed following administration of 3000 mg/kg p.o. to mice. Another specifically claimed compound from this series of 3-alkylpyrrolo[3,2-*c*]quinoline derivatives is:



285146: C₂₀ H₁₇ F N₂ O

SOURCE – Korea Research Institute of Chemical Technology, Taejon (KR).

REFERENCES

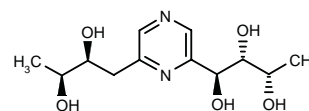
1. Choi, J.-K. et al. (Korea Research Institute of Chemical Technology) *3-Alkyl-pyrrolo[3,2-*c*]quinoline derivs*. WO 0001696.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

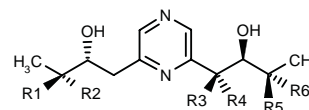
285455

1-[6-[2(*S*),3(*S*)-Dihydroxybutyl]pyrazin-2-yl]butane-1(*S*),2(*R*),3(*S*)-triol

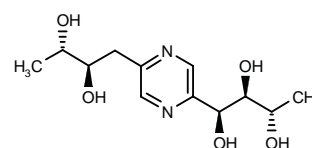


C₁₂ H₂₀ N₂ O₅; Mol wt: 272.2990

ACTION – Hypoglycemic agent reported to be active by the oral route and which exhibits weak toxicity ($LD_{50} > 2000$ mg/kg p.o. in mice). Other specifically claimed compounds from this series of polyhydroxyalkylpyrazine derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
285456	H	OH	H	OH	OH	H	C ₁₂ H ₂₀ N ₂ O ₅
285457	OH	H	OH	H	H	OH	C ₁₂ H ₂₀ N ₂ O ₅



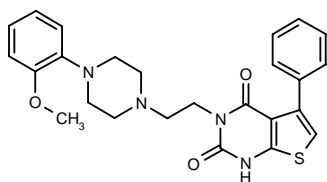
285458: C₁₂ H₂₀ N₂ O₅

SOURCE – Aventis Pharma.

REFERENCES

1. Bashiardes, G. et al. (Aventis Pharma SA) *Polyhydroxyalkylpyrazine derivs. and their preparation and medicines containing them*. FR 2781155, WO 0004002.

ACTION – Agent for the treatment of benign prostatic hyperplasia (BPH), detrusor instability and incontinence, an α_1 -adrenoceptor antagonist with some degree of selectivity for the α_{1d} subtype (rat; $K_i = 0.361$ nM) over α_{1a} (rat; $K_i = 0.578$ nM) and α_{1b} subtypes (hamster; $K_i = 1.86$ nM). *In vivo*, compound was found to inhibit epinephrine-induced increases in intraurethral pressure in dogs with a pA_2 value of 8.47 versus 6.97 and 8.91 for terazosin and tamsulosin, respectively. Compound exhibited weaker hypotensive properties than terazosin and tamsulosin in a spontaneously hypertensive rat (SHR) model, giving a pED_{50} value of 6.04 versus pED_{50} values of 6.40 and 7.22, respectively, for reference compounds. Another compound from this series of piperazinyl- pyrimidinedione derivatives is:



285462: C₂₅ H₂₆ N₄ O₃ S

SOURCE – Abbott.

REFERENCES

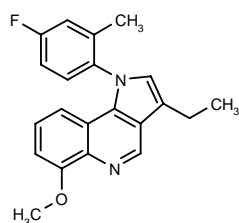
1. Meyer, M.D. and Carroll, W.A. (Abbott Laboratories Inc.) *Piperazinyl pyrimidine dione cpds. selective for adrenoceptors*. WO 0004027.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

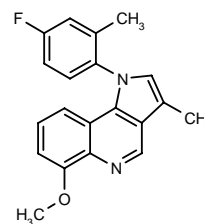
285145

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C₂₁ H₁₉ F N₂ O; Mol wt: 334.3921

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285146: C₂₀ H₁₇ F N₂ O

SOURCE – Korea Research Institute of Chemical Technology, Taejon (KR).

REFERENCES

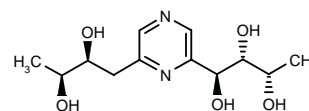
1. Choi, J.-K. et al. (Korea Research Institute of Chemical Technology) *3-Alkyl-pyrrolo[3,2-*c*]quinoline derivs*. WO 0001696.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

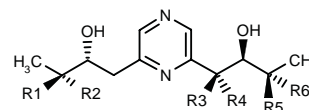
285455

1-[6-[2(*S*),3(*S*)-Dihydroxybutyl]pyrazin-2-yl]butane-1(*S*),2(*R*),3(*S*)-triol

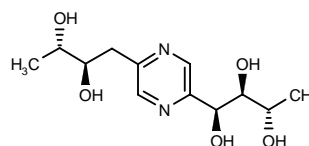


C₁₂ H₂₀ N₂ O₅; Mol wt: 272.2990

ACTION – Hypoglycemic agent reported to be active by the oral route and which exhibits weak toxicity ($LD_{50} > 2000$ mg/kg p.o. in mice). Other specifically claimed compounds from this series of polyhydroxyalkylpyrazine derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
285456	H	OH	H	OH	OH	H	C ₁₂ H ₂₀ N ₂ O ₅
285457	OH	H	OH	H	H	OH	C ₁₂ H ₂₀ N ₂ O ₅



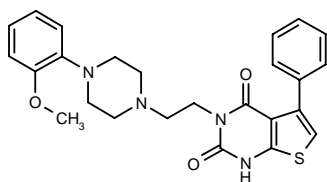
285458: C₁₂ H₂₀ N₂ O₅

SOURCE – Aventis Pharma.

REFERENCES

1. Bashiardes, G. et al. (Aventis Pharma SA) *Polyhydroxyalkylpyrazine derivs. and their preparation and medicines containing them*. FR 2781155, WO 0004002.

ACTION – Agent for the treatment of benign prostatic hyperplasia (BPH), detrusor instability and incontinence, an α_1 -adrenoceptor antagonist with some degree of selectivity for the α_{1d} subtype (rat; $K_i = 0.361$ nM) over α_{1a} (rat; $K_i = 0.578$ nM) and α_{1b} subtypes (hamster; $K_i = 1.86$ nM). *In vivo*, compound was found to inhibit epinephrine-induced increases in intraurethral pressure in dogs with a pA_2 value of 8.47 versus 6.97 and 8.91 for terazosin and tamsulosin, respectively. Compound exhibited weaker hypotensive properties than terazosin and tamsulosin in a spontaneously hypertensive rat (SHR) model, giving a pED_{50} value of 6.04 versus pED_{50} values of 6.40 and 7.22, respectively, for reference compounds. Another compound from this series of piperazinyl- pyrimidinedione derivatives is:



285462: C₂₅ H₂₆ N₄ O₃ S

SOURCE – Abbott.

REFERENCES

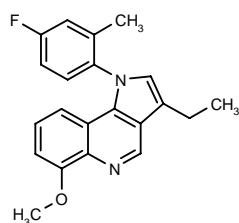
1. Meyer, M.D. and Carroll, W.A. (Abbott Laboratories Inc.) *Piperazinyl pyrimidine dione cpds. selective for adrenoceptors*. WO 0004027.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

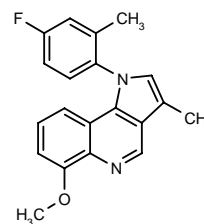
285145

3-Ethyl-1-(4-fluoro-2-methylphenyl)-6-methoxy-1*H*-pyrrolo[3,2-*c*]quinoline



C₂₁ H₁₉ F N₂ O; Mol wt: 334.3921

ACTION – Antiulcer agent that inhibits gastric acid secretion and is reported to exhibit excellent stability. Compound was found to be more potent than omeprazole in inhibiting H^+/K^+ -ATPase *in vitro*, as well as ethanol-induced gastric ulcers in fasted rats following oral administration. No toxicity was observed following administration of 3000 mg/kg p.o. to mice. Another specifically claimed compound from this series of 3-alkylpyrrolo[3,2-*c*]quinoline derivatives is:



285146: C₂₀ H₁₇ F N₂ O

SOURCE – Korea Research Institute of Chemical Technology, Taejon (KR).

REFERENCES

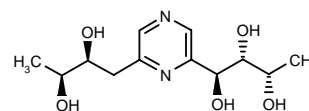
1. Choi, J.-K. et al. (Korea Research Institute of Chemical Technology) *3-Alkyl-pyrrolo[3,2-*c*]quinoline derivs*. WO 0001696.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

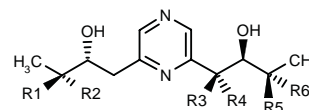
285455

1-[6-[2(*S*),3(*S*)-Dihydroxybutyl]pyrazin-2-yl]butane-1(*S*),2(*R*),3(*S*)-triol

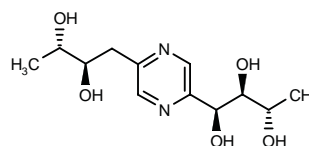


C₁₂ H₂₀ N₂ O₅; Mol wt: 272.2990

ACTION – Hypoglycemic agent reported to be active by the oral route and which exhibits weak toxicity ($LD_{50} > 2000$ mg/kg p.o. in mice). Other specifically claimed compounds from this series of polyhydroxyalkylpyrazine derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
285456	H	OH	H	OH	OH	H	C ₁₂ H ₂₀ N ₂ O ₅
285457	OH	H	OH	H	H	OH	C ₁₂ H ₂₀ N ₂ O ₅



285458: C₁₂ H₂₀ N₂ O₅

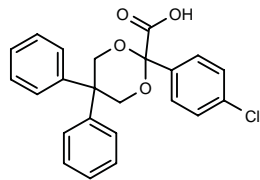
SOURCE – Aventis Pharma.

REFERENCES

1. Bashiardes, G. et al. (Aventis Pharma SA) *Polyhydroxyalkylpyrazine derivs. and their preparation and medicines containing them*. FR 2781155, WO 0004002.

285561

2-(4-Chlorophenyl)-5,5-diphenyl-1,3-dioxane-2-carboxylic acid



C23 H19 Cl O4; Mol wt: 394.8521

ACTION – Potent peroxisome proliferator-activated receptor PPAR α and PPAR γ activator with potential in the treatment or prevention of dyslipidemia, atherosclerosis and diabetes. Compound markedly increased the expression of the acyl-CoA oxidase (ACO) gene in rat hepatocytes (427 \pm 63% at 25 μ M vs. 100% in controls) and of the chloramphenicol acetyltransferase (CAT) reporter gene in COS cells, indicating PPAR α and PPAR γ receptor activation, respectively. When tested *in vivo* in *db/db* mice, compound was shown to significantly reduce glycemia (36 and 24% on day 3 and 15, respectively), triglycerides (40% on day 15) and free fatty acids (27% on day 15) at a dose of 100 mg/kg/day p.o. x 15 days.

SOURCE – Merck KGaA.

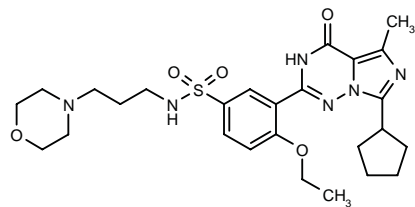
REFERENCES

1. Berthelon, J.-J. et al. (Merck Patent GmbH) *Cyclic cpds. useful in the treatment of dyslipidaemia, atherosclerosis and diabetes, pharmaceutical compsns. and preparation process.* FR 2781222, WO 0004011.

TREATMENT OF MALE SEXUAL DYSFUNCTION

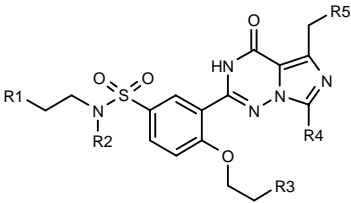
284983

3-(7-Cyclopentyl-5-methyl-4-oxo-3,4-dihydroimidazo-[5,1-f][1,2,4]triazin-2-yl)-4-ethoxy-N-[3-(4-morpholinyl)-propyl]benzenesulfonamide



C26 H36 N6 O5 S; Mol wt: 544.6734

ACTION – An inhibitor of cGMP-phosphodiesterases (PDE), particularly PDE1 and PDE5, claimed for the treatment of cardiovascular disorders, erectile dysfunction and female sexual dysfunction and for use as a smooth muscle-relaxing agent. Other representative compounds within this series of 7-alkyl- and cycloalkyl-substituted imidazotriazinone derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
284985	-N(CH2CH2OH)CH2CH2-		H	cyclopentyl	H	C ₂₅ H ₃₄ N ₆ O ₅ S
284986	3,4-(MeO)2-Ph	Me	H	cyclopentyl	H	C ₃₀ H ₃₇ N ₆ O ₆ S
284987	-N(CH2CH2OH)CH2CH2-		Me	cyclopentyl	H	C ₂₅ H ₃₄ N ₆ O ₅ S
284988	-N(CH2CH2OH)CH2CH2-		H	CH(Et)2	H	C ₂₅ H ₃₆ N ₆ O ₅ S
284990	-N(CH2CH2OH)CH2CH2-		H	CH(Et)C6H13	H	C ₂₉ H ₄₄ N ₆ O ₅ S
284991	3,4-(MeO)2-Ph	Me	H	CH(Et)C6H13	H	C ₃₄ H ₄₇ N ₆ O ₆ S
284992	3,4-(MeO)2-Ph	Me	Me	CH(Et)C6H13	H	C ₃₅ H ₄₉ N ₆ O ₆ S
284993	-N(CH2CH2OH)CH2CH2-		Me	CH(Et)C6H13	H	C ₃₀ H ₄₆ N ₆ O ₅ S
284994	3,4-(MeO)2-Ph	Me	H	cycloheptyl	H	C ₃₂ H ₄₁ N ₆ O ₆ S
284995	-N(CH2CH2OH)CH2CH2-		H	CH(Pr)2	H	C ₂₇ H ₄₀ N ₆ O ₅ S
284996	3,4-(MeO)2-Ph	Me	H	CH(Pr)2	H	C ₃₂ H ₄₃ N ₆ O ₆ S
284997	-N(CH2CH2OH)CH2CH2-		H	cycloheptyl	H	C ₂₇ H ₃₈ N ₆ O ₅ S
284998	3,4-(MeO)2-Ph	Me	H	cycloheptyl	H	C ₃₂ H ₄₁ N ₆ O ₆ S
284999	-N(Me)CH2CH2-		H	cyclopentyl	Me	C ₂₅ H ₃₄ N ₆ O ₄ S
285000	-N(CH2CH2OH)CH2CH2-		H	cyclopentyl	Me	C ₂₆ H ₃₆ N ₆ O ₅ S

SOURCE – Bayer.

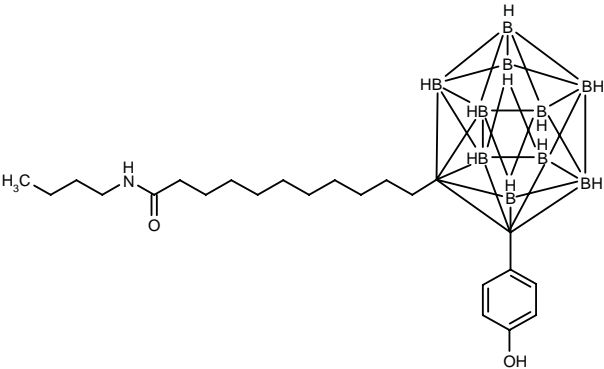
REFERENCES

1. Niewöhner, U. et al. (Bayer AG) *7-Alkyl- and cycloalkyl-substd. imidazotriazinones.* DE 19827640, WO 9967244.

TREATMENT OF GYNECOLOGICAL DISORDERS

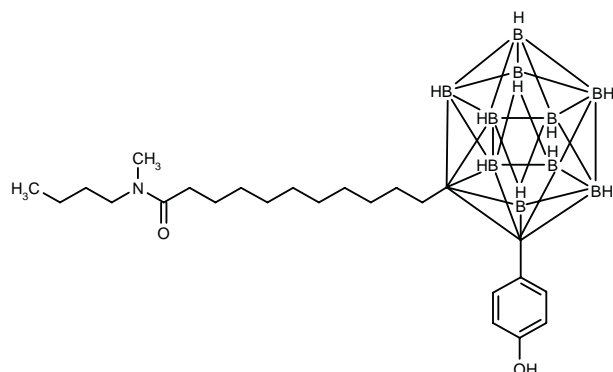
285572

N-Butyl-11-[2-(4-hydroxyphenyl)-1,2-dicarba-closo-dodecaborane(12)-1-yl]undecanamide



C23 H45 B10 N O2; Mol wt: 475.7235

ACTION – Estrogen receptor (ER) antagonist proven to inhibit in a concentration-dependent manner (0.01-0.1 μ M) the transcriptional activity of 17 β -estradiol in a luciferase reporter gene assay using COS-1 cells transfected with a rat ER α expression plasmid, although it was less potent than ICI-182780. Potentially useful as a lead compound for the design of more potent and selective antiestrogenic agents. Within this series of hydrophobic pharmacophores based on the carborane skeleton, the following is also included:



285573: C₂₄ H₄₇ B₁₀ N O₂

SOURCE – University of Tokyo, Tokyo (JP).

REFERENCES

1. Endo, Y. et al. *New estrogenic antagonists bearing dicarba-closo-dodecaborane as a hydrophobic pharmacophore*. Chem Pharm Bull 2000, 48(2): 312.

CONTRACEPTIVES

OVALBUMIN-LHRH-7

285048

Chimeric polypeptide having seven LHRH inserts in an ovalbumin carrier protein

ACTION – Chimeric protein consisting of a carrier protein with potential antigenic sites and luteinizing hormone-releasing hormone (LHRH), for use as a contraceptive vaccine. Compound was shown to induce high anti-LHRH titers and to significantly reduce uterine-ovarian weight in female mice, with or without adjuvant. Additionally, all heifers immunized with compound (1 primary + 2 booster immunizations at 5-week intervals, with adjuvant) exhibited suppression of ovulation between about days 110-160 from primary immunization and were infertile during this time; these effects were shown to be reversible.

SOURCE – Washington State University, Pullman, WA (US).

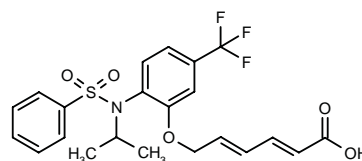
REFERENCES

1. Reeves, J.J. et al. (Washington State University) *Chimeric contraceptive vaccines*. US 6013770.

UTERINE STIMULANTS AND TOCOLYTICS

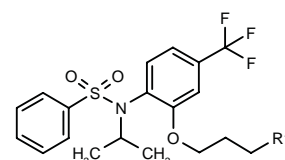
285428

6-[2-[*N*-(Isopropyl)phenylsulfonamido]-5-(trifluoromethyl)phenoxy]-2,4-hexadienoic acid



C₂₂ H₂₂ F₃ N O₅ S; Mol wt: 469.4778

ACTION – Agent that binds to prostanoid EP₁ receptors (K_i = 0.026 μ M for the murine EP₁ receptor expressed in CHO cells), potentially useful for inhibiting or inducing uterine contractions, inhibiting or promoting gastrointestinal motility, inhibiting gastric acid secretion, increasing bladder volume, reducing blood pressure and for inducing analgesia, sleep and diuresis. Other compounds from this series of sulfonamide derivatives include the following:



Compound	R1	Formula
285429	CH=CHCO ₂ H	C ₂₂ H ₂₄ F ₃ NO ₅ S
285430	CH ₂ CH=CHCO ₂ H	C ₂₃ H ₂₆ F ₃ NO ₅ S
285431	CH ₂ CO ₂ H	C ₂₁ H ₂₄ F ₃ NO ₅ S
285432	CH ₂ CH ₂ CO ₂ H	C ₂₂ H ₂₆ F ₃ NO ₅ S

SOURCE – Ono.

REFERENCES

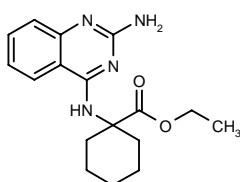
1. Ohuchida, S. and Nagao, Y. (Ono Pharmaceutical Co., Ltd.) *Sulfonamide derivs. and agents containing them as active ingredient*. JP 2000007646.

DERMATOLOGIC DRUGS

TREATMENT OF ALLERGIC SKIN DISORDERS

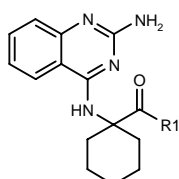
285107

1-(2-Aminoquinazolin-4-ylamino)cyclohexanecarboxylic acid ethyl ester



C₁₇H₂₂N₄O₂; Mol wt: 314.3868

ACTION – Agent for the treatment of allergic and autoimmune diseases and AIDS that inhibits Th2-type cytokine and IgE production. Compound produced concentration-dependent inhibition of IL-4 and IL-5 production in murine lymph node cells at 0.625-10.0 μ M, giving an IC₅₀ for IL-4 production of 2.0 μ M. It also significantly inhibited IgE production in ovalbumin-sensitized mice, giving 82% inhibition at a dose of 20 mg/kg/day p.o. x 12 days. When tested in a model of TNCB-induced contact dermatitis in mice, it was found to reduce hapten-induced dermal hypertrophy following topical administration. A representative compound from a series of quinazoline derivatives, wherein the following are also included:



Compound	R1	Formula
285108	OMe	C ₁₈ H ₂₀ N ₄ O ₂
285109	Pr	C ₁₈ H ₂₄ N ₄ O
285110	OPr	C ₁₈ H ₂₄ N ₄ O ₂
285111	allyl-O	C ₁₈ H ₂₂ N ₄ O ₂

SOURCES – Sumitomo Chemical; Sumitomo Pharmaceuticals.

REFERENCES

1. Tokunaga, T. et al. (Sumitomo Pharmaceuticals Co., Ltd.; Sumitomo Chemical Co., Ltd.) *Quinazoline derivs.* JP 1999335360.

ANTIPSORIATICS

ISIS-18268

285563

20-Mer antisense oligonucleotide whose sequence is: 5'-TCTGAGTAGCAGAGGAGCTC-3', with alternating phosphorothioate/phosphodiester linkages, in which all the nucleosides are 2'-O-(2-methoxyethyl)nucleosides and the cytidines in positions 2, 10 and 18 are also 5-methylcytidines

ACTION – Nuclease-resistant antisense oligonucleotide containing staggered phosphorothioate/phosphodiester linkages, targeted to human ICAM-1. Compound concentration-dependently inhibited ICAM-1 expression in human umbilical vein endothelial cells (HUVEC), giving about 90% inhibition at a concentration of 40 nM, and was shown to display pharmacokinetic and tissue distribution properties in rats intermediate between those of phosphodiester and phosphorothioate oligonucleotides following i.v. administration. Potentially useful in the treatment of inflammatory skin disorders, including psoriasis and contact dermatitis.

SOURCE – Isis Pharmaceuticals.

REFERENCES

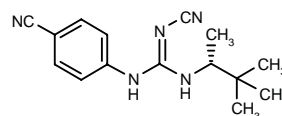
1. Manoharan, M. (Isis Pharmaceuticals, Inc.) *Carbohydrate or 2'-modified oligonucleotides having alternating internucleoside linkages.* WO 0003720.

HAIR GROWTH STIMULANTS

285198

2-Cyano-1-(4-cyanophenyl)-3-[1(*R*),2,2-trimethylpropyl]guanidine

4-[2-Cyano-3-[1(*R*),2,2-trimethylpropyl]guanidino]benzonitrile



C₁₅H₁₉N₅; Mol wt: 269.3501

ACTION – Hair growth promoter for use in male pattern baldness, the (*R*)-enantiomer of a known potassium channel opener* that has been found to possess superior properties compared to the (*S*)-enantiomer and the racemic mixture. When tested in male C3H mice, compound was shown to be about 8 times more effective than the (*S*)-enantiomer in stimulating hair follicles to produce hair growth following topical application, and it exhibited a faster onset of action.

SOURCE – Bristol-Myers Squibb.

REFERENCES

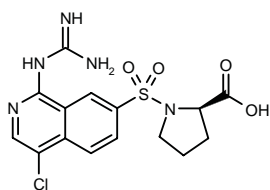
1. Atwal, K.S. (Bristol-Myers Squibb Co.) *Enantiomers of 4-[[[(cyanoimino)[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile*. US 6013668.

*See **BMS-182264** Drug Data Rep 1992, 014(04): 0318.

WOUND-HEALING AGENTS

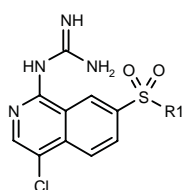
285694

N-(4-Chloro-1-guanidinoisoquinolin-7-ylsulfonyl)-D-proline



C15 H16 Cl N5 O4 S; Mol wt: 397.8414

ACTION – Reversible and competitive urokinase (urinary-type plasminogen activator, or uPA) inhibitor ($K_i < 20$ nM) with selectivity relative to tissue-type plasminogen activator (tPA) and plasmin. Potentially useful for wound healing, chronic dermal ulcers, angiogenesis, bone restructuring, embryo implantation in the uterus, cell infiltration into sites of inflammation, ovulation, spermatogenesis, psoriasis, tissue remodeling during wound repair and organ differentiation, fibrosis, local invasion of tumors into adjacent areas, secondary metastatic spread of tumor cells and tissue destruction in arthritis. Other specifically claimed compounds from this series of isoquinoline derivatives include the following:



Compound	R1	Formula
285695	1-[N(Me)2CH2CH2NHCO]-cyclopentyl	C ₂₀ H ₂₇ ClN ₆ O ₃ S
285696	2(R)-(t-BuOCO)-1-Pip	C ₂₀ H ₂₆ ClN ₆ O ₄ S
285697	1-(4-morpholinyl-CO)-cyclopentyl-NH	C ₂₀ H ₂₅ ClN ₆ O ₄ S
285698	10-oxo-9-oxa-6-azaspiro[4.5]dec-6-yl	C ₁₈ H ₂₀ ClN ₅ O ₄ S

SOURCE – Pfizer.

REFERENCES

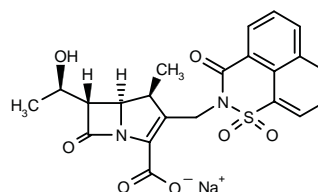
1. Barber, C.G. et al. (Pfizer Inc.;Pfizer Ltd.) *Isoquinolines as urokinase inhibitors*. WO 0005214.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

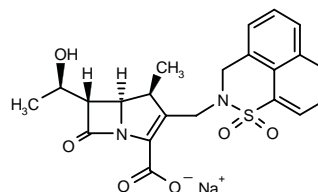
284951

(1*S*,5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-(1,1,3-trioxo-2,3-dihydronaphtho[1,8-*de*]-1,2-thiazin-2-ylmethyl)-1-carba-2-penem-3-carboxylic acid sodium salt

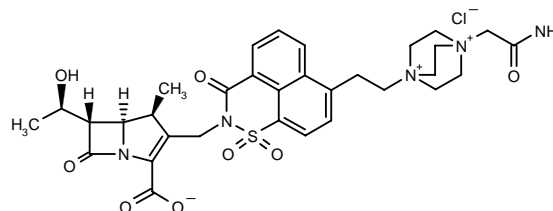


C22 H19 N2 Na O7 S; Mol wt: 478.4551

ACTION – Carbapenem antibiotic active against Gram-positive microorganisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other exemplified compounds within this series of carbapenems substituted with a 1,1-dioxo-2,3-dihydronaphtho[1,8-*de*][1,2]thiazin-2-ylmethyl or 1,1,3-trioxo-2,3-dihydronaphtho[1,8-*de*][1,2]thiazin-2-ylmethyl moiety include the following:



284952: C22 H21 N2 Na O6 S



284953: C32 H38 Cl N5 O8 S

SOURCE – Merck & Co.

REFERENCES

1. Ratcliffe, R.W. et al. (Merck & Co., Inc.) *Naphtho[1,8-de]thiazin-2-yl methyl carbapenem antibacterials*. WO 9967242.

SOURCE – Bristol-Myers Squibb.

REFERENCES

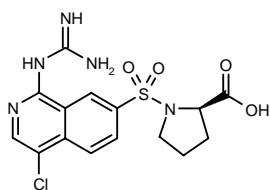
1. Atwal, K.S. (Bristol-Myers Squibb Co.) *Enantiomers of 4-[[[(cyanoimino)[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile*. US 6013668.

*See **BMS-182264** Drug Data Rep 1992, 014(04): 0318.

WOUND-HEALING AGENTS

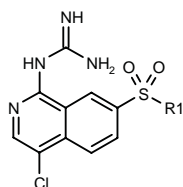
285694

N-(4-Chloro-1-guanidinoisoquinolin-7-ylsulfonyl)-D-proline



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Compound	R1	Formula
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285696	2(R)-(t-BuOCO)-1-Pip	C ₂₀ H ₂₆ ClN ₆ O ₄ S
285697	1-(4-morpholinyl-CO)-cyclopentyl-NH	C ₂₀ H ₂₅ ClN ₆ O ₄ S
285698	10-oxo-9-oxa-6-azaspiro[4.5]dec-6-yl	C ₁₈ H ₂₀ ClN ₅ O ₄ S

SOURCE – Pfizer.

REFERENCES

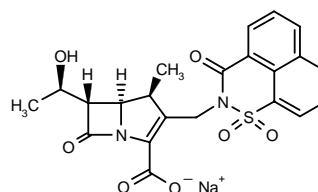
1. Barber, C.G. et al. (Pfizer Inc.;Pfizer Ltd.) *Isoquinolines as urokinase inhibitors*. WO 0005214.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

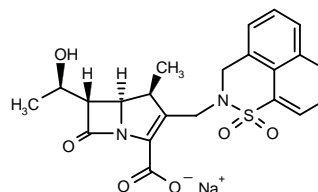
284951

(1*S*,5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-(1,1,3-trioxo-2,3-dihydronaphtho[1,8-*de*]-1,2-thiazin-2-ylmethyl)-1-carba-2-penem-3-carboxylic acid sodium salt

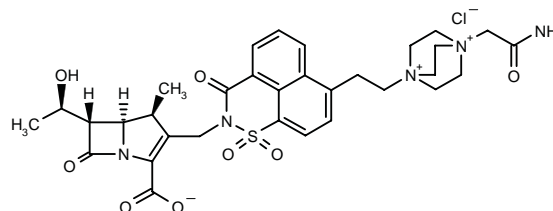


C22 H19 N2 Na O7 S; Mol wt: 478.4551

ACTION – Carbapenem antibiotic active against Gram-positive microorganisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other exemplified compounds within this series of carbapenems substituted with a 1,1-dioxo-2,3-dihydronaphtho[1,8-*de*][1,2]thiazin-2-ylmethyl or 1,1,3-trioxo-2,3-dihydronaphtho[1,8-*de*][1,2]thiazin-2-ylmethyl moiety include the following:



284952: C22 H21 N2 Na O6 S



284953: C32 H38 Cl N5 O8 S

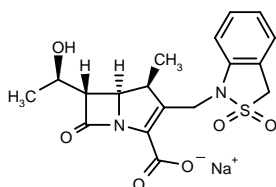
SOURCE – Merck & Co.

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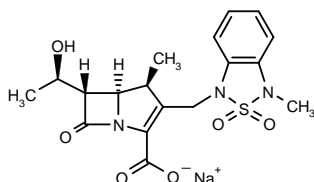
284961

(1*S*,5*R*,6*S*)-2-(2,2-Dioxo-1,3-dihydrobenzo[*c*]isothiazol-1-ylmethyl)-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid sodium salt

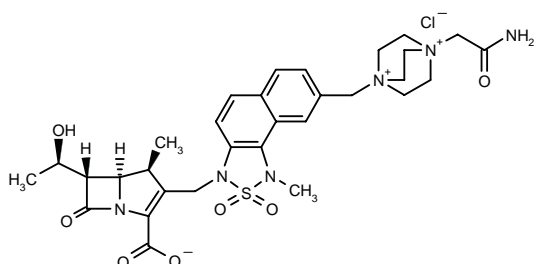


C₁₈ H₁₉ N₂ Na O₆ S; Mol wt: 414.4121

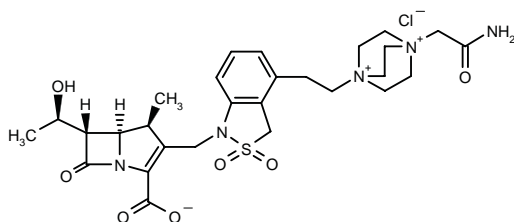
ACTION – Carbapenem antibiotic active against Gram-positive microorganisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other exemplified compounds within this series of heterocyclymethyl-substituted carbapenems include the following:



284962: C₁₈ H₂₀ N₃ Na O₆ S



284963: C₃₁ H₃₉ Cl N₆ O₇ S



284964: C₂₈ H₃₈ Cl N₅ O₇ S

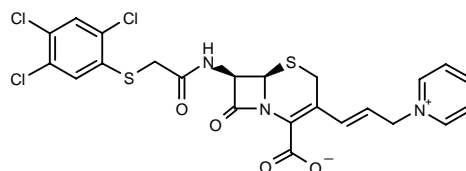
SOURCE – Merck & Co.

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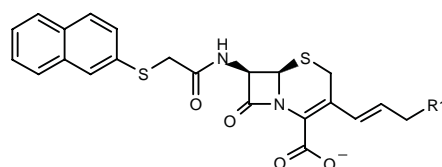
284965

(6*R*,7*R*)-7-[2-(2,4,5-Trichlorophenylsulfanyl)acetamido]-3-[3-(pyridinium-1-yl)-1(*E*)-propenyl]-3-cephem-4-carboxylate



C₂₃ H₁₈ Cl₃ N₃ O₄ S₂; Mol wt: 570.9032

ACTION – Cephalosporin antibiotic especially active against Gram-positive microorganisms including methicillin-sensitive (MSSA) and methicillin-resistant staphylococci (MRSA), enterococci and pneumococci. Compound gave MIC values against *Staphylococcus aureus* 6538 (MSSA), *S. aureus* 270A (MRSA), *Enterococcus faecalis* 6 and *Streptococcus pneumoniae* 907 of < 0.1, 1, 0.25 and < 0.1 µg/ml, respectively. In addition, synergistic antibacterial activity against MRSA was observed in combination with imipenem (4 µg/ml), with a reduction in MIC values against *S. aureus* 42080 and *S. aureus* SPO-19 of from 8 µg/ml to 1 µg/ml and from 4 µg/ml to 0.5 µg/ml, respectively. Other exemplified compounds from this series of propenyl cephalosporin derivatives include the following:



Compound	R1	Formula
284966	1-Pyr	C ₂₇ H ₂₃ N ₃ O ₄ S ₂
284967	4-aza-1-azoniabicyclo[2.2.2]oct-1-yl	C ₂₈ H ₃₀ N ₄ O ₄ S ₂
284968	N+(Me)2CH2CH2CH2OH	C ₂₇ H ₃₁ N ₃ O ₅ S ₂

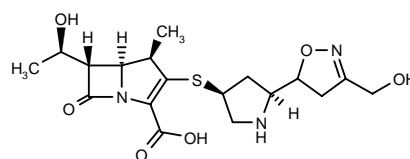
SOURCE – Roche.

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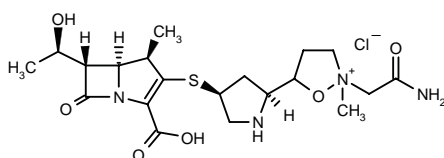
285303

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-[5(*S*)-[3-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl]pyrrolidin-3(*S*)-ylsulfanyl]-1-methyl-1-carba-2-penem-3-carboxylic acid isomer 1



C₁₈ H₂₅ N₃ O₆ S; Mol wt: 411.4765

ACTION – Carbapenem antibiotic with broad-spectrum antibacterial activity against Gram-positive and Gram-negative isolates including *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Salmonella typhimurium*, *Enterobacter cloacae* and *Klebsiella aerogenes* (MIC = 0.013-0.098 µg/ml), as well as *Pseudomonas aeruginosa* (MIC = 0.195-0.391 µg/ml). When compared to meropenem, it showed superior antibacterial activity, particularly against *S. aureus*, and higher dehydropeptidase-I (DHP-I) stability. Another 1β-methylcarbapenem with similar activity is:



285306: C20 H31 Cl N4 O6 S

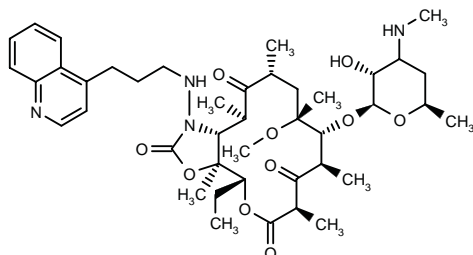
SOURCE – LG Chem.

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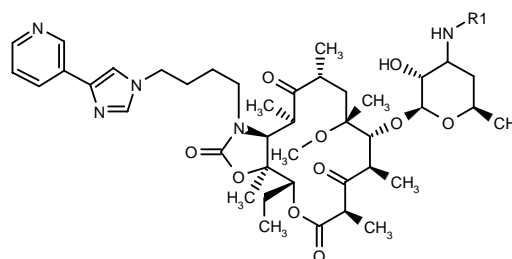
285362

N'-Demethyl-3-des(hexopyranosyloxy)-11-deoxy-6-*O*-methyl-3-oxo-11-[3-(quinolin-4-yl)propylhydrazino]erythromycin A 11-*N'*,12-*O*-cyclic carbamate



C42 H62 N4 O10; Mol wt: 782.9698

ACTION – Antibacterial erythromycin derivative with potent activity against Gram-positive bacteria such as *Staphylococcus aureus* 011UC4 (MIC = 0.080 µg/ml), *Staphylococcus epidermidis* 012GO11i (MIC = 0.300 µg/ml), *Streptococcus pyogenes* 02A1UC1 (MIC = 0.040 µg/ml), *Streptococcus agalactiae* 02B1HT1 (MIC = 0.020 µg/ml), *Enterococcus faecalis* 02D2UC1 (MIC = 0.040 µg/ml), *Enterococcus faecium* 02D3HT1 (MIC = 0.040 µg/ml) and *Streptococcus pneumoniae* 032UC1 (MIC = 0.01 µg/ml or less). Also reported to be active against *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia*, *Legionella*, *Ureaplasma*, *Toxoplasma* and *Mycobacterium* spp. Other specifically claimed compounds from this series of erythromycin derivatives include the following:



Compound	R1	Formula
285363	Me	C ₄₂ H ₆₃ N ₅ O ₁₀
285364	H	C ₄₁ H ₆₁ N ₅ O ₁₀

SOURCE – Aventis Pharma.

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GRANULYSIN

285463

Antimicrobial protein produced by human cytolytic T-lymphocytes and natural killer cells

ACTION – Antimicrobial protein produced by cytolytic T-lymphocytes and NK cells, with broad-spectrum antimicrobial activity including Gram-positive and Gram-negative bacteria, fungi and parasites. Compound was also extremely active against both extracellular and intracellular forms of *Mycobacterium tuberculosis*. Although it is unable to reach the intracellular compartment alone, it appears to interact with lipids in the bacterial cell wall, leading to degradation. Considered a prototype compound for a new class of antibiotics.

SOURCE – Stanford University, Stanford, CA (US).

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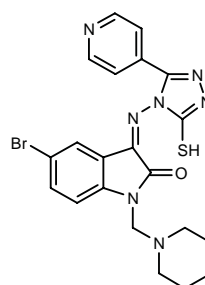
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*See **187116** (see **183442**) Drug Data Rep 1992, 014(09): 0821.

ANTIBACTERIAL DRUGS

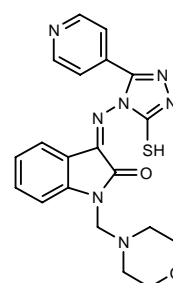
285079

5-Bromo-1-(1-piperidinylmethyl)-3-[3-(4-pyridyl)-5-sulfanyl-4*H*-1,2,4-triazol-4-ylimino]-2,3-dihydro-1*H*-indol-2-one



C21 H20 Br N7 O S; Mol wt: 498.4070

ACTION – Antibacterial agent with slight to moderate activity against a panel of Gram-positive and Gram-negative bacteria including *Vibrio cholerae* non-01, *Enterococcus faecalis* and *Bacillus subtilis* (MIC = 4.88 µg/ml). Compound also exhibited moderate antifungal activity against a number of fungi including *Microsporum audouinii*, *Trichophyton mentagrophytes*, *Microsporum gypseum* and *Epidermophyton floccosum* (MIC = 9.76 µg/ml). Another isatin derivative is:



285078: C20 H19 N7 O2 S

SOURCES – Banaras Hindu University, Varanasi (IN); Rega Institute for Medical Research, Leuven (BE).

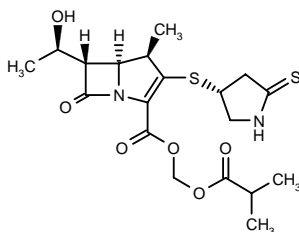
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TA-949

284982

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[2-thioxo-pyrrolidin-4(*R*)-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid isobutyryloxymethyl ester



C19 H26 N2 O6 S2; Mol wt: 442.5544

ACTION – Orally active 1β-methylcarbapenem antibiotic, a prodrug of a known compound* proven to have broad-spectrum antibacterial activity *in vitro* against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* (MIC = 0.05-0.1 µg/ml), *Staphylococcus epidermidis* (MIC = 0.05 µg/ml), *Escherichia coli* (MIC = 0.013 µg/ml or less), *Proteus mirabilis* (MIC = 0.05 µg/ml), *Proteus vulgaris* (MIC = 0.025 µg/ml) and *Pseudomonas aeruginosa* (MIC = 12.5-25 µg/ml). The prodrug showed good oral activity in mice infected with *S. aureus* Smith (ED₅₀ = 0.46 mg/kg) and was devoid of acute toxicity at up to 4000 mg/kg p.o.

SOURCE – Tanabe Seiyaku.

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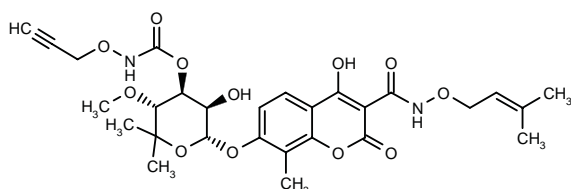
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285312

N-(2-Propynyloxy)carbamic acid 6(*R*)-[3-[*N*-(3-methyl-2-butenyl)carbamoyl]-4-hydroxy-8-methyl-2-oxo-2*H*-1-benzopyran-7-yloxy]-5(*R*)-hydroxy-3(*R*)-methoxy-2,2-dimethyltetrahydro-2*H*-pyran-4(*S*)-yl ester

7-[6-Deoxy-4-*O*,5-*C*-dimethyl-3-*O*-[*N*-(2-propynyloxy)-carbamoyl]- α -L-mannopyranosyloxy]-4-hydroxy-8-methyl-2-oxo-2*H*-1-benzopyran-3-carbohydroxamic acid 3-methyl-2-butenyl ester



C28 H34 N2 O12; Mol wt: 590.5786

ACTION – Coumarin antibacterial agent, an inhibitor of *Staphylococcus aureus* DNA gyrase B with good antibacterial activity against wild-type *Streptococcus pyogenes* and *Staphylococcus aureus* (MIC = 0.08 and 0.04 μ g/ml or less, respectively), novobiocin-resistant *S. aureus* (MIC = 0.6 μ g/ml), oxacillin-resistant *Staphylococcus epidermidis* (MIC = 0.15 μ g/ml) and multidrug-resistant *Enterococcus faecium* and *S. aureus* (MIC = 0.3 and 0.04 μ g/ml or less, respectively).

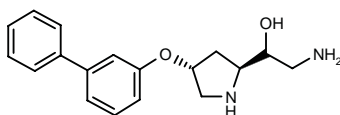
SOURCE – Aventis Pharma.

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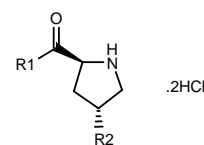
285670

2-Amino-1-[4(*R*)-(3-biphenyloxy)pyrrolidin-2(*S*)-yl]-ethanol

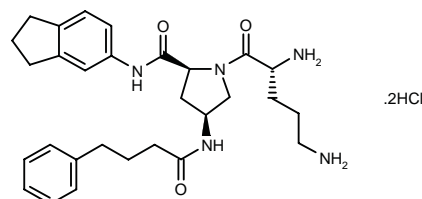


C18 H22 N2 O2; Mol wt: 298.3838

ACTION – Efflux pump inhibitor that is able to potentiate the activity of coadministered antibacterial agents, as demonstrated against *Pseudomonas aeruginosa* PAM1001 when given together with levofloxacin (100% growth inhibition at 2.5 μ g/ml + 0.25 μ g/ml levofloxacin vs. controls receiving only levofloxacin). Other related compounds are:



Compound	R1	R2	Formula
285725	4-(3-Cl-2-Me-Ph)-1-Piz	CH2NH2	C ₁₇ H ₂₇ Cl ₃ N ₄ O
285727	4-[3,5-(Cl)2-PhO]-1-Pip	NHCOCH2NH2	C ₁₈ H ₂₆ Cl ₄ N ₄ O ₃



285726: C29 H41 Cl2 N5 O3

SOURCES – Daiichi Pharmaceutical; Microcide.

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GATIFLOXACIN

Prop INN; USAN

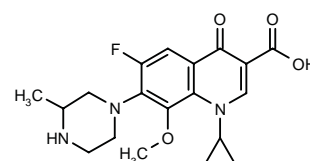
137307

(\pm)-1-Cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

AM-1155⁺

BMS-206584

CG-5501



C19 H22 F N3 O4; Mol wt: 375.4030

ACTION – Broad-spectrum fluoroquinolone antibacterial agent.

INDICATION – Treatment of acute bacterial sinusitis, community-acquired pneumonia, acute bacterial exacerbations of chronic bronchitis, uncomplicated urinary tract infections (UTIs), complicated UTIs, pyelonephritis and uncomplicated urethral and cervical gonorrhea.

PRESENTATION – Tablets, 200 and 400 mg; single-use vials for i.v. administration, 200 mg/20 ml and 400 mg/40 ml; flexible premix bags, 200 mg/100 ml and 400 mg/200 ml.

PROPRIETARY NAME – Tequin (US).

SOURCES – Bristol-Myers Squibb (licensed from Kyorin); copromoted by Schering-Plough.

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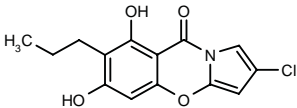
*Drug Data Rep 1991, 013(01): 0064.

STREPTOPYRROLE¹⁻⁵

285130

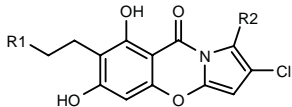
2-Chloro-6,8-dihydroxy-7-propyl-9H-pyrrolo[2,1-b][1,3]-benzoxazin-9-one

XR-587



C14 H12 Cl N O4; Mol wt: 293.7048

ACTION – Antimicrobial and antineoplastic agent isolated from the fermentation broth of *Streptomyces rimosus*, with growth-inhibitory activity against Gram-positive bacteria such as *Bacillus subtilis* NCIMB 8054 (MIC = 0.78 µg/ml) and three strains of *Staphylococcus aureus* including two drug-resistant strains (MIC = 0.2-0.78 µg/ml). Compound was also active against the yeast *Cryptococcus neoformans* NCPF 3379 (MIC = 0.78 µg/ml) and against some strains of *Candida* including *Candida guilliermondii*, *Candida kefyr*, *Candida parapsilosis* and *Candida stellatoidea* (MIC = 6.25-12.5 µg/ml). It was shown to inhibit bacterial histidine kinase activity with an IC₅₀ of 20 µM and exhibited cytotoxic activity towards a number of human cancer cell lines including ovarian carcinoma A2780, lung carcinoma A549, colon carcinoma HT29/219, chronic myelogenous leukemia K562, breast adenocarcinoma MCF-7 and melanoma SK-MEL-28 (IC₅₀ = 12.7-71.7 µM). Other halogenated compounds extracted from the fermentation of *S. rimosus* are:



Compound	R1	R2	Formula
285131 ^{1,2,5}	H	H	C ₁₃ H ₁₀ ClNO ₄
285132 ^{1,2,5}	Me	Cl	C ₁₄ H ₁₁ Cl ₂ NO ₄
285133 ^{1,2,5}	H	Cl	C ₁₃ H ₉ Cl ₂ NO ₄
285134 ^{1,2,5}	Et	H	C ₁₅ H ₁₄ ClNO ₄

SOURCES – Warner-Lambert; Xenova.

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3. Breinholt, J. et al. Streptopyrrole: An antimicrobial metabolite from Streptomyces armeniacus. Acta Chem Scand 1998, 52(8): 1040.

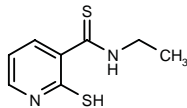
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ANTIMYCOBACTERIAL AGENTS

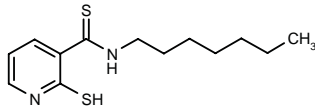
284937

N-Ethyl-2-sulfanylpuridine-3-carbothioamide



C8 H10 N2 S2; Mol wt: 198.3130

ACTION – Antimycobacterial agent active against *Mycobacterium tuberculosis* and *Mycobacterium avium* complex including both laboratory strains and clinical isolates (MIC = 0.5-8 µg/ml). It had low acute toxicity in rats and mice both after p.o. and i.p. administration (LD₅₀ > 200 and > 2000 mg/kg, respectively), but pharmacokinetic studies indicated that it may not have suitable properties for oral or parenteral administration, i.e., it was rapidly cleared following i.v. dosing and plasma levels were below the limits of detection following oral dosing. Another related compound is:



284938: C13 H20 N2 S2

SOURCES – Universidad del País Vasco, Vitoria (ES); Università degli Studi di Milano, Milano (IT); Università degli Studi di Pavia, Pavia (IT).

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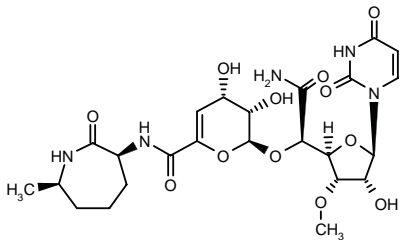
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A-500359A

285392

2(*S*)-[1(*R*)-Carbamoyl-1-[5(*R*)-(uracil-1-yl)-4(*R*)-hydroxy-3(*S*)-methoxytetrahydro-2(*S*)-furanyl]methoxy]-3(*S*),4(*S*)-dihydroxy-*N*-[7(*R*)-methyl-2-oxoperhydroazepin-3(*S*)-yl]-3,4-dihydro-2*H*-pyran-6-carboxamide

5'(*R*)-Carbamoyl-3'-*O*-methyl-5'-*O*-[6-[*N*-[7(*R*)-methyl-2-oxoperhydroazepin-3(*S*)-yl]carbamoyl]-3(*S*),4(*S*)-dihydroxy-3,4-dihydro-2*H*-pyran-2(*S*)-yl]uridine



C24 H33 N5 O12; Mol wt: 583.5477

ACTION – Antibacterial agent isolated from a culture of *Streptomyces griseus* SANK-60196 (FERM BP-5420), an analogue of capuramycin with higher potency *in vitro* against *Mycobacterium smegmatis* SANK-75075 (MIC = 6.2 µg/ml vs. 12.5 µg/ml for capuramycin).

SOURCE – Sankyo.

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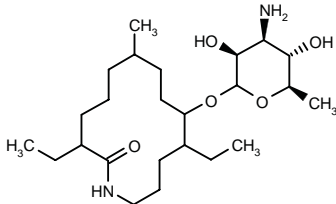
1. Inukai, M. et al. (Sankyo Co., Ltd.) *Novel antibacterial cpds.* WO 0002892.

ANTIFUNGAL AGENTS

285353

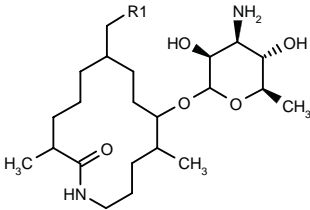
9-(3-Amino-3,6-dideoxy-D-mannopyranosyloxy)-2,10-diethyl-6-methyl-13-tridecanolactam

10-(3-Amino-3,6-dideoxy-D-mannopyranosyloxy)-3,11-diethyl-7-methyl-1-azacyclotetradecan-2-one



C24 H46 N2 O5; Mol wt: 442.6364

ACTION – Macrolactam monosaccharide isolated from an antimicrobial complex produced by cultures of *Actinomadura fulva* subsp. *uruguayensis* SCC 1778 (ATCC 53713) with antifungal activity, particularly against *Candida* strains. Other compounds isolated from the same source are:



Compound	R1	Formula
285354	H	C ₂₂ H ₄₂ N ₂ O ₅
285355	Me	C ₂₃ H ₄₄ N ₂ O ₅

SOURCE – Schering-Plough.

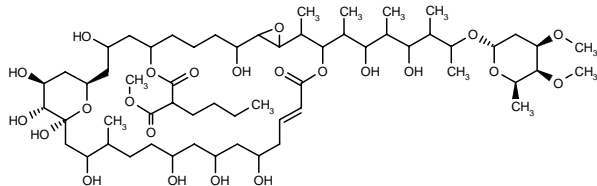
REFERENCES

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BRASILINOLIDE B

285139

(30*S*,31*R*,32*S*,34*R*)-2-Butylpropanedioic acid 1-[14-(6-(2,6-dideoxy-3,4-*O*-dimethyl-β-D-*lyxo*-hexopyranosyloxy)-2,4-dihydroxy-1,3,5-trimethylheptyl]-3,9,20,22,24,28,30,31,32-nonahydroxy-13,27-dimethyl-16-oxo-11,15,34-trioxatricyclo[28.3.1.0^{10,12}]tetratriacont-17-en-5-yl] 3-methyl diester



C59 H104 O23; Mol wt: 1181.4480

ACTION – Macrolide antifungal agent extracted from *Nocardia brasiliensis* that displays activity against a range of fungi including *Aspergillus niger*, *Aspergillus fumigatus*, *Candida parapsilosis*, *Candida albicans*, *Candida krusei*, *Candida glabrata* and *Cryptococcus neoformans* (MIC = 12.5-25 µg/ml); it was also active against a *C. albicans* azole-type antifungal-resistant strain (MIC = 25 µg/ml). No immunosuppressive activity was seen at up to 10 µg/ml.

SOURCE – Higeta Shoyu.

REFERENCES

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ANTIVIRAL DRUGS

285049

20-Mer oligonucleotide whose sequence is: 5'-GGGGGA-GGATGCTGAGGGGG-3', in which the internucleoside linkages between positions 1-2, 2-3, 3-4, 10-11, 12-13, 17-18, 18-19 and 19-20 are phosphorothioate

ACTION – Antisense oligonucleotide for the treatment of diseases caused by viruses such as HIV, herpes simplex virus (HSV-1, HSV-2), influenza, varicella-zoster virus, hepatitis B and papillomavirus; when tested *in vitro* against HSV-1 in monkey kidney Vero cell cultures, compound exhibited an MIC of 3 µM, whereas the maximum tolerated dose (MTD) was > 80 µM. Another oligonucleotide from this series of G CAP-stabilized oligonucleotides is:

23-Mer oligonucleotide whose sequence is: 5'-GGGGGAGGATGCTGAGGAGGGGG-3', in which the internucleoside linkages between positions 1-2, 2-3, 3-4, 10-11, 12-13, 13-14, 20-21, 21-11 and 22-23 are phosphorothioate

285050

Other oligonucleotides within the scope of the patent are reported to be useful for the treatment or prevention of cancer, restenosis, diseases mediated by integrins or cell–cell adhesion receptors, or diseases triggered by factors such as TNF-α.

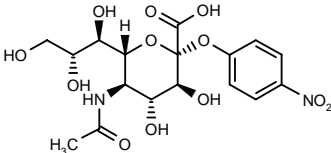
SOURCE – Aventis Pharma.

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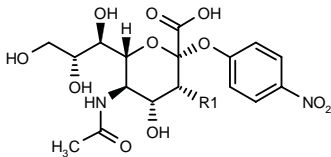
285135

N-Acetyl-3(S)-hydroxy-2-O-(4-nitrophenyl)neuraminic acid



C17 H22 N2 O12; Mol wt: 446.3628

ACTION – Antiviral agent that is believed to act by inhibiting both the hemagglutinin and sialidase membrane proteins of influenza virus. Other compounds from this series of sialic acid derivatives include the following:



Compound	R1	Formula
285137	F	C ₁₇ H ₂₁ FN ₂ O ₁₁
285138	OH	C ₁₇ H ₂₂ N ₂ O ₁₂
285140	NH2	C ₁₇ H ₂₃ N ₃ O ₁₁

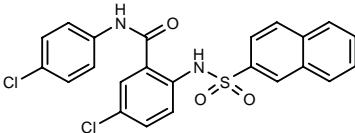
SOURCE – Institute of Physical and Chemical Research (RIKEN), Saitama (JP).

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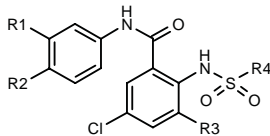
285438

5-Chloro-N-(4-chlorophenyl)-2-(2-naphthylsulfonamido)-benzamide



C23 H16 Cl2 N2 O3 S; Mol wt: 471.3624

ACTION – Agent for the treatment of hepatitis C that inhibits hepatitis C virus (HCV) protease, giving 22, 84 and 100% inhibition of the enzyme at 1, 10 and 100 µM, respectively. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
285439	H	Cl	H	1-Naph	C ₂₃ H ₁₆ Cl ₂ N ₂ O ₃ S
285440	H	Cl	H	5-N(Me)2-1-Naph	C ₂₅ H ₂₁ Cl ₂ N ₃ O ₃ S
285441	H	OPh	H	2-Naph	C ₂₉ H ₂₁ ClN ₂ O ₄ S
285443	H	2,4,6-(Cl)3-PhO	H	2-Naph	C ₂₉ H ₁₈ Cl ₄ N ₂ O ₄ S
285445	H	4-Cl-PhO	H	2-Naph	C ₂₉ H ₂₀ Cl ₂ N ₂ O ₄ S
285447	H	C5H11	H	2-Naph	C ₂₈ H ₂₇ ClN ₂ O ₃ S
285449	OPh	H	H	2-Naph	C ₂₉ H ₂₁ ClN ₂ O ₄ S
285450	H	SMe	H	2-Naph	C ₂₄ H ₁₉ ClN ₂ O ₃ S ₂
285451	H	C12H25	H	2-Naph	C ₃₅ H ₄₁ ClN ₂ O ₃ S
285452	H	C8H17	H	2-Naph	C ₃₁ H ₃₃ ClN ₂ O ₃ S
285453	OPh	H	Cl	2-Naph	C ₂₉ H ₂₀ Cl ₂ N ₂ O ₄ S
285454	OPh	H	H	5-N(Bu)2-1-Naph	C ₃₇ H ₃₉ ClN ₃ O ₄ S

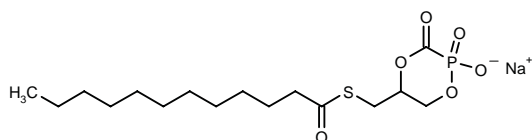
SOURCE – Ajinomoto.

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285789

5-(Dodecanoylsulfanylmethyl)-2,3-dioxo-1,4,2-dioxaphosphinan-2-olate sodium salt



C16 H28 Na O6 P S; Mol wt: 402.4212

ACTION – Antiviral agent, a potential cyclic diester foscarnet prodrug proven to inhibit herpes simplex virus (HSV-1) replication in human fibroblasts with an EC_{50} value of 256 μ M, with comparable activity to foscarnet itself. Studies on the metabolism of the prodrug in intestinal and liver homogenates showed almost no conversion of the prodrug to foscarnet, indicating either that homogenate incubation does not accurately represent the metabolism of the foscarnet ester, or that the prodrug could exert antiviral activity via an alternative mechanism.

SOURCE – AstraZeneca.

REFERENCES

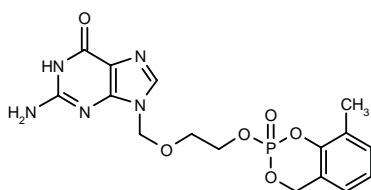
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2. Ferguson, C.G. et al. *Design of novel derivatives of phosphonoformate (foscarnet) as prodrugs and antiviral agents.* J Org Chem 2000, 65(4): 1218.

3-METHYL-CYCLOSAL-ACVMP

281254

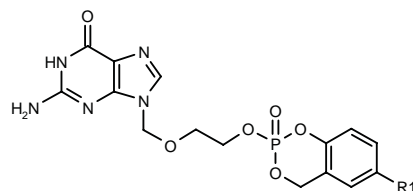
2-Amino-9-[2-(8-methyl-2-oxo-4*H*-1,3,2-benzodioxaphosphinin-2-yloxy)ethoxymethyl]-1,9-dihydro-6*H*-purin-6-one

9-[2-(8-Methyl-2-oxo-4*H*-1,3,2-benzodioxaphosphinin-2-yloxy)ethoxymethyl]guanine



C16 H18 N5 O6 P; Mol wt: 407.3212

ACTION – Antiviral agent, an acyclic nucleoside analogue related to aciclovir proven to be active against herpes simplex virus (HSV-1) replication in Vero cells (EC_{50} = 0.47-0.61 and 0.51-1.62 μ M against wild-type and thymidine kinase-negative HSV-1, respectively), as well as against Epstein-Barr virus (EBV) in the P3HR-1 cell line, as demonstrated by inhibition of viral DNA synthesis and viral capsid antigen expression (IC_{50} = 2.38 and 9.17 μ g/ml, respectively); no cytotoxicity was seen in either cell line at up to 100 μ M. When compared to the parent compound aciclovir, it was equally active against wild-type HSV-1 and EBV, but in contrast, it retained the same antiviral potency against TK- HSV-1 strains. Within this series of cycloSal-pro-nucleotides, the following are also included:



Compound	R1	Formula
5-Methyl-cycloSal-ACVMP [281255]	Me	C ₁₆ H ₁₈ N ₅ O ₆ P
cycloSal-ACVMP [281257]	H	C ₁₅ H ₁₆ N ₅ O ₆ P

SOURCES – Friedrich-Schiller-Universität, Jena (DE); Julius-Maximilians-Universität, Würzburg (DE).

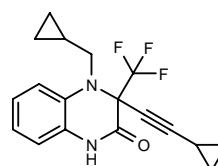
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AIDS MEDICINES

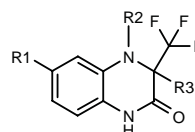
285008

3-(2-Cyclopropylethynyl)-4-(cyclopropylmethyl)-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoxalin-2-one



C18 H17 F3 N2 O; Mol wt: 334.3393

ACTION – Antiviral agent for AIDS, an HIV reverse transcriptase inhibitor. Other specifically claimed compounds from this series of substituted quinoxalin-2(1*H*)-ones include the following:



Compound	R1	R2	R3	Formula
285009	H	Me	Bu	C ₁₄ H ₁₇ F ₃ N ₂ O
285012	F	allyl	cyclopropyl-ethynylene	C ₁₇ H ₁₄ F ₄ N ₂ O
285014	Cl	cyclopropyl-CH2	cyclopropyl-ethynylene	C ₁₈ H ₁₆ ClF ₃ N ₂ O
285015	H	CO2Et	cyclopropyl-ethynylene	C ₁₇ H ₁₅ F ₃ N ₂ O ₃
285016	H	CO2C(Me)=CH2	cyclopropyl-ethynylene	C ₁₈ H ₁₅ F ₃ N ₂ O ₃
285017	H	CO2Me	cyclopropyl-ethynylene	C ₁₆ H ₁₃ F ₃ N ₂ O ₃
285019	F	CO2C(Me)=CH2	cyclopropyl-ethynylene	C ₁₈ H ₁₄ F ₄ N ₂ O ₃

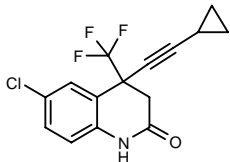
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Patel, M. and McHugh, R.J. (DuPont Pharmaceuticals Co.) *Substd. quinoxalin-2(1H)-ones useful as HIV reverse*. WO 0000478.

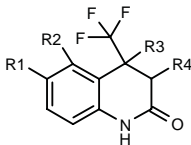
285062

6-Chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-one



C15 H11 Cl F3 N O; Mol wt: 313.7049

ACTION – Antiviral agent for AIDS, an HIV reverse transcriptase inhibitor. Other specifically claimed compounds from this series of substituted quinolin-2(1H)-ones include the following:



Compound	R1	R2	R3	R4	Formula
285063	F	F	cyclopropyl-ethynylene	H	C ₁₅ H ₁₀ F ₅ NO
285064	Cl	H	cyclopropyl-ethynylene	Me	C ₁₆ H ₁₃ ClF ₃ NO
285065	Cl	H	cyclopropyl-ethynylene	i-Pr	C ₁₈ H ₁₇ ClF ₃ NO
285066	Cl	H	cyclopropyl-ethynylene	allyl	C ₁₈ H ₁₅ ClF ₃ NO
285067	Cl	H	cyclopropyl-ethynylene	CH ₂ Ph	C ₂₂ H ₁₇ ClF ₃ NO
285068	Cl	H	cyclopropyl-ethynylene	OH	C ₁₅ H ₁₁ ClF ₃ NO ₂
285069	Cl	H	cyclopropyl-ethynylene	CO ₂ Me	C ₁₇ H ₁₃ ClF ₃ NO ₃
285070	Cl	H	cyclopropyl-CH=CH	H	C ₁₅ H ₁₃ ClF ₃ NO
285071	Cl	H	cyclopropyl-CH ₂ CH ₂	H	C ₁₅ H ₁₅ ClF ₃ NO
285072	F	F	cyclopropyl-CH=CH	H	C ₁₅ H ₁₂ F ₅ NO
285073	F	F	cyclopropyl-CH ₂ CH ₂	H	C ₁₅ H ₁₄ F ₅ NO

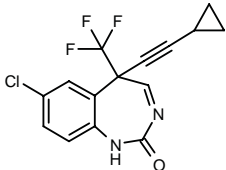
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Patel, M. and Rodgers, J.D. (DuPont Pharmaceuticals Co.) *Substd. quinolin-2(1H)-ones useful as HIV reverse transcriptase inhibitors*. WO 0000475.

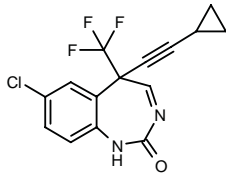
285075

(±)-7-Chloro-5-(2-cyclopropylethynyl)-5-(trifluoromethyl)-2,5-dihydro-1H-1,3-benzodiazepin-2-one



C15 H10 Cl F3 N2 O; Mol wt: 326.7040

ACTION – Antiviral agent for AIDS, an HIV reverse transcriptase inhibitor. Other specifically claimed compounds from this series of 1,3-benzodiazepin-2-ones and 1,3-benzoxazepin-2-ones include the following:



Compound	Isomer	Formula
285076	S	C ₁₅ H ₁₀ ClF ₃ N ₂ O
285077	R	C ₁₅ H ₁₀ ClF ₃ N ₂ O

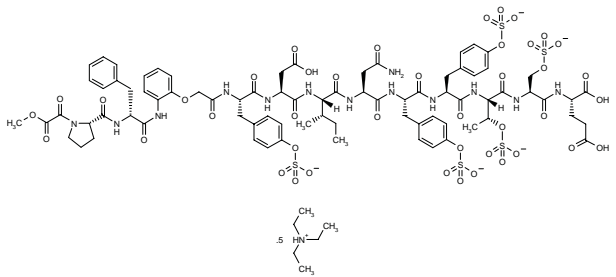
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Rodgers, J.D. and Cocuzza, A.J. (DuPont Pharmaceuticals Co.) *1,3-Benzodiazepin-2-ones and 1,3-benzoxazepin-2-ones useful as HIV reverse transcriptase inhibitors*. WO 0000479.

285571

N-[2-[2-[1-(Methoxyoxalyl)-L-prolyl-D-phenylalanyl-amido]phenoxy]acetyl]-O-sulfo-L-tyrosyl-L-aspartyl-L-isoleucyl-L-asparaginy-O-sulfo-L-tyrosyl-O-sulfo-L-tyrosyl-O-sulfo-L-threonyl-O-sulfo-L-seryl-L-glutamic acid pentakis(triethylammonium) salt



C78 H90 N13 O42 S5 . 5 C6 H16 N; Mol wt: 2552.9450

ACTION – Anti-HIV agent, a peptide that mimics the chemokine receptor CCR5 and exerts significant anti-HIV-1 activity at 200 and 1000 µg/ml and no significant cytotoxicity at these concentrations.

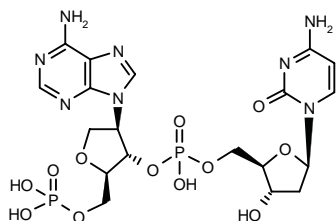
SOURCES – Gunma University, Gunma (JP); University of Shizuoka, Shizuoka (JP).

REFERENCES

1. Konishi, K. et al. *Synthesis of peptides mimicking chemokine receptor CCR5 and their inhibitory effects against HIV-1 infection*. Chem Pharm Bull 2000, 48(2): 308.

285754

5'-O-[[2-(Adenin-9-yl)-1,2-dideoxy-5-O-(phosphonoxy)-D-arabinofuranos-3-yloxy](hydroxy)phosphoryl]-2-deoxycytidine



C₁₉ H₂₆ N₈ O₁₂ P₂; Mol wt: 620.4064

ACTION – Anti-HIV phosphorylated dinucleotide with strong inhibitory activity against recombinant wild-type HIV integrase (IC₅₀ = 19 and 25 μM, respectively, for 3' processing and strand transfer activities). Compound binds to the catalytic core of integrase, the inhibition of integrase is metal-dependent and the internucleotide bond exhibits resistance to cleavage by mammalian phosphodiesterases.

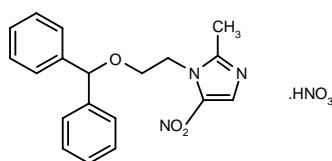
SOURCES – University of Iowa, Iowa City, IA (US); National Cancer Institute, Bethesda, MD (US).

REFERENCES

1. Taktakishvili, M. et al. *Recognition and inhibition of HIV integrase by a novel dinucleotide*. Bioorg Med Chem Lett 2000, 10(3): 249.

285755

1-[2-(Diphenylmethoxy)ethyl]-2-methyl-5-nitro-1H-imidazole nitrate



C₁₉ H₁₉ N₃ O₃ · H N O₃; Mol wt: 400.3890

M.p. 139-41 °C.

ACTION – Anti-HIV agent, a non-nucleotide reverse transcriptase inhibitor (IC₅₀ = 50 nM) able to protect MT-4 cells from HIV-1 infection with the same potency as nevirapine (EC₅₀ = 0.2 and 0.3 μM, respectively); it did not show cytotoxicity at up to 200 μM and did not inhibit HIV-1 or HIV-2 replication in chronically infected H9/IIIB cells. Selected for further study.

SOURCES – Università degli Studi di Cagliari, Cagliari (IT); Università degli Studi "La Sapienza", Roma (IT); Università degli Studi di Siena, Siena (IT).

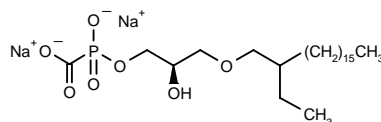
REFERENCES

1. Silvestri, R. et al. *1-[2-(Diphenylmethoxy)ethyl]-2-methyl-5-nitroimidazole: A potent lead for the design of novel NNRTIs*. Bioorg Med Chem Lett 2000, 10(3): 253.

EB-PFA

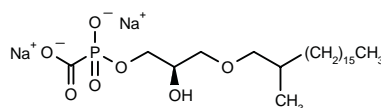
285185

[3-(2-Ethyl-octadecyloxy)-2(*R*)-hydroxypropoxy]-(hydroxy)phosphorylcarboxylic acid disodium salt



C₂₄ H₄₇ Na₂ O₇ P; Mol wt: 524.5823

ACTION – Anti-HIV agent, a foscarnet analogue with dramatically improved potency against HIV-1 replication in MT-2 cells (IC₅₀ = 0.39 μM vs. 16.3 μM for foscarnet) and against a panel of drug-resistant HIV strains including those resistant to nucleoside analogue reverse transcriptase inhibitors such as zidovudine and lamivudine, and other dideoxynucleosides such as didanosine, zalcitabine and stavudine (IC₅₀ = 0.32-1.34 μM). Highly synergistic activity was also seen in combination with zidovudine against nonresistant strains. Preliminary studies in mice demonstrated that compound was absorbed orally. Another alkylglycerol foscarnet analogue is:



MB-PFA [285184]: C₂₃ H₄₅ Na₂ O₇ P

SOURCES – University of California, San Diego, La Jolla, CA (US); University of Pittsburgh, Pittsburgh, PA (US); Veterans Administration Medical Center, Hartford, VT (US).

REFERENCES

1. Hammond, J.L. et al. *Selection of HIV-1 variants resistant to potent lipid prodrugs of phosphonoformic acid*. 7th Conf Retroviruses Opportunistic Infect (Jan 30-Feb 2, San Francisco) 2000, Abst 736.

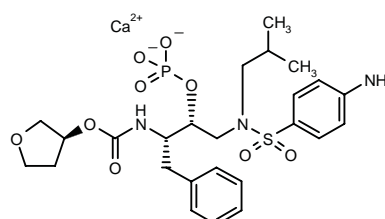
2. Hostettler, K.Y. et al. *Alkylglycerol foscarnet analogs are active in vitro at submicromolar concentrations against a panel of drug-resistant strains of HIV-1*. 7th Conf Retroviruses Opportunistic Infect (Jan 30-Feb 2, San Francisco) 2000, Abst 666.

GW-433908G

285394

N-[3-[*N*-(4-Aminophenylsulfonyl)-*N*-isobutylamino]-1(*S*)-benzyl-2(*R*)-(phosphonoxy)propyl]carbamic acid tetrahydrofuran-3(*S*)-yl ester calcium salt

GW-433908 (as free acid)



C₂₅ H₃₄ Ca N₃ O₉ P S; Mol wt: 623.6736

ACTION – Anti-HIV agent, a calcium salt of the amprenavir phosphate ester prodrug GW-433908A⁺. The new salt was evaluated in a single-dose pharmacokinetic study in healthy volunteers administered tablets or capsules (suspension) equivalent to 1200 mg amprenavir. In the fasting state, it was bioequivalent to amprenavir and food did not affect its pharmacokinetics; in the presence of a low-fat meal, compound was 23% more bioavailable than amprenavir.

SOURCES – Glaxo Wellcome; Vertex.

REFERENCES

1. Armitage, I.G. et al. (Glaxo Group Ltd.) *Calcium (3S) tetrahydro-3-furanyl(1S,2R)-3-[[[(4-aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonoxy)-propyl]carbamate*. WO 0004033.
2. Brouwer, K.R. and Polli, J.W. (Glaxo Group Ltd.) *Methods and compsns. for increasing penetration of HIV protease inhibitors*. WO 9964001.
3. Hale, M.R. et al. (Vertex Pharmaceuticals Inc.) *Prodrugs of aspartyl protease inhibitors*. WO 9933792.
4. Hale, M.R. et al. (Vertex Pharmaceuticals Inc.) *Prodrugs of aspartyl protease inhibitors*. WO 9933793.
5. Falcoz, C. et al. *Food effect on single dose pharmacokinetics of GW433908G, a prodrug of amprenavir (141w94, Apv) administered as a tablet to healthy male subjects*. 37th Annu Meet Infect Dis Soc Am (Nov 18-21, Philadelphia) 1999, Abst 343.
6. Spaltenstein, A. et al. *Highly polar, water-soluble prodrugs of amprenavir: A new approach toward a more compact dosing regimen*. 7th Conf Retroviruses Opportunistic Infect (Jan 30-Feb 2, San Francisco) 2000, Abst 505.

*Drug Data Rep 2000, 022(01): 0075.

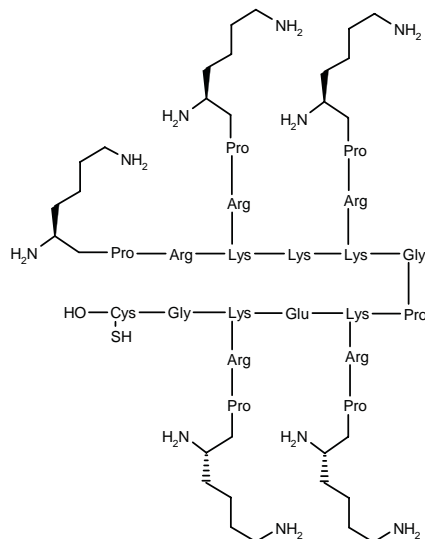
HB-19

281451

N^2, N^6 -[*H*-L-Lys[ψ(CH₂N)]-L-Pro-L-Arg]-L-Lys-L-Lys- N^6 -[*H*-L-Lys[ψ(CH₂N)]-L-Pro-L-Arg]-L-Lys-Gly-L-Pro- N^6 -[*H*-L-Lys[ψ(CH₂N)]-L-Pro-L-Arg]-L-Lys-L-Glu- N^6 -[*H*-L-Lys[ψ(CH₂N)]-L-Pro-L-Arg]-L-Lys-Gly-L-Cys-OH

N^2, N^6 -Bis[1-[(2*S*)-2,6-diaminohexyl]-L-prolyl-L-arginyl]-L-lysyl-L-lysyl- N^6 -[1-[(2*S*)-2,6-diaminohexyl]-L-prolyl-L-arginyl]-L-lysylglycyl-L-prolyl- N^6 -[1-[(2*S*)-2,6-diaminohexyl]-L-prolyl-L-arginyl]-L-lysyl-L-α-glutamyl- N^6 -[1-[(2*S*)-2,6-diaminohexyl]-L-prolyl-L-arginyl]-L-lysylglycyl-L-cysteine

5[Kψ(CH₂N)PR]-TASP



C132 H252 N50 O23 S; Mol wt: 2939.8360

ACTION – Anti-HIV V3 loop-mimicking pseudopeptide that specifically inhibits HIV infection in different CD4⁺ cell lines, primary T-lymphocytes and macrophages (IC₅₀ = 0.1-0.5 μM) by binding to the cell surface and blocking the attachment of HIV particles to permissive cells. In intact cells, compound irreversibly binds nucleolins and forms a complex with cell surface-expressed nucleolin, which causes its eventual degradation. Compound showed good stability in serum and represents a potential candidate for clinical development.

SOURCES – CNRS; Institut Pasteur, Paris (FR).

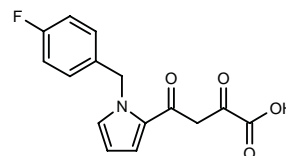
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2. Callebaut, C. et al. *Inhibition of HIV infection by pseudopeptides blocking viral envelope glycoprotein-mediated membrane fusion and cell death*. Virology 1996, 218(1): 181.
3. Callebaut, C. et al. *Pseudopeptide TASP inhibitors of HIV entry bind specifically to a 95-kDa cell surface protein*. J Biol Chem 1997, 272(11): 7159.
4. Nisole, S. et al. *The anti-HIV pseudopeptide HB-19 forms a complex with the cell-surface-expressed nucleolin independent of heparan sulfate proteoglycans*. J Biol Chem 1999, 374(39): 27875.
5. Seddiki, N. et al. *The V3 loop-mimicking pseudopeptide 5[Kpsi(CH₂N)PR]-TASP inhibits HIV infection in primary macrophage cultures*. AIDS Res Hum Retroviruses 1999, 15(4): 381.

L-731988*,1,3

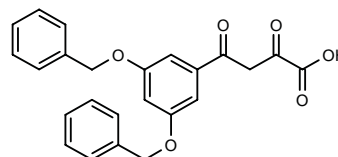
283999

4-[1-(4-Fluorobenzyl)-1*H*-pyrrol-2-yl]-2,4-dioxobutyric acid



C15 H12 F N O4; Mol wt: 289.2608

ACTION – Anti-HIV agent, an HIV-1 integrase inhibitor, as demonstrated in a strand transfer assay using recombinant integrase (IC₅₀ = 50 nM) and by inhibition of the formation of HIV-1 preintegration complexes (IC₅₀ = 80 nM), proven to inhibit HIV-1 replication in cell culture (IC₅₀ = 1-2 μM). Compound showed activity against clinical isolates and variants resistant to reverse transcriptase and protease inhibitors. It inhibited viral DNA integration without affecting HIV-1 DNA synthesis or processing in infected cells. Another related compound is:



L-708906 [284453],2,3:** C24 H20 O6

SOURCES – Merck & Co.; Tularik.

REFERENCES

1. Selnick, H.G. et al. (Merck & Co., Inc.;Tularik Inc.) *HIV integrase inhibitors*. WO 9962513.
2. Young, S.D. et al. (Merck & Co., Inc.;Tularik Inc.) *HIV integrase inhibitors*. WO 9962520.
3. Hazuda, D.J. et al. *Inhibitors of strand transfer that prevent integration and inhibit HIV-1 replication in cells*. Science 2000, 287(5453): 646.

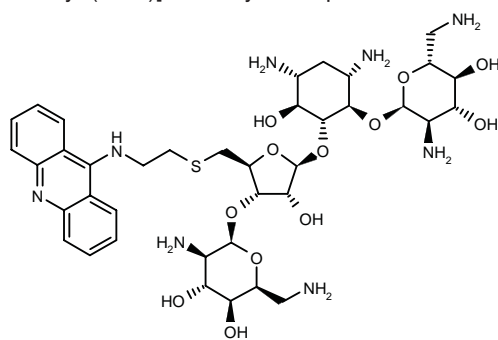
*Identified compound **283999** published with incorrect structure and chemical name Drug Data Rep 2000, 022(02): 0172.

Identified compound **284453 Drug Data Rep 2000, 022(02): 0172.

NEOMYCIN-ACRIDINE

285372

O-2,6-Diamino-2,6-dideoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-O-[O-2,6-diamino-2,6-dideoxy- β -L-idopyranosyl-(1 \rightarrow 3)]5-[2-(acridin-9-ylamino)ethylsulfanyl]-5-deoxy- β -D-ribofuranosyl-(1 \rightarrow 5)]-2-deoxy-D-streptamine



C38 H58 N8 O12 S; Mol wt: 850.9862

ACTION – Anti-HIV agent that competitively blocks the binding of the Rev protein to its RNA recognition element known as the Rev Response Element (RRE; IC_{50} = 0.65 μ M), by competitively binding to the same region of RRE as the Rev peptide. The affinity of compound for RRE is only 2-fold lower than that of the Rev peptide (K_i = 1.5 and 1 nM for compound and Rev peptide, respectively).

SOURCE – University of California, San Diego, La Jolla, CA (US).

REFERENCES

1. Kirk, S.R. et al. *Neomycin-acridine conjugate: A potent inhibitor of Rev-RRE binding*. J Am Chem Soc 2000, 122(5): 980.

T-1249

274850

N-Acetyl-L-tryptophyl-L-glutaminy-L-glutamyl-L-tryptophyl-L-glutamyl-L-glutaminy-L-lysyl-L-isoleucyl-L-threonyl-L-alanyl-L-leucyl-L-leucyl-L-glutamyl-L-glutaminy-L-alanyl-L-glutaminy-L-isoleucyl-L-glutaminy-L-glutaminy-L-glutamyl-L-lysyl-L-asparaginy-L-glutamyl-L-tyrosyl-L-glutamyl-L-leucyl-L-glutaminy-L-lysyl-L-leucyl-L-aspartyl-L-lysyl-L-tryptophyl-L-alanyl-L-seryl-L-leucyl-L-tryptophyl-L-glutamyl-L-tryptophyl-L-phenylalaninamide

C235 H341 N57 O67; Mol wt: 5036.6110

ACTION – Anti-HIV agent, an HIV fusion inhibitor that binds to a region of the HIV gp41 surface protein. In preclinical tests compound was seen to strongly inhibit HIV-1 replication via inhibition of cell-cell fusion using both laboratory strains and clinical isolates including zidovudine-, saquinavir- and T-20-resistant strains. In addition, compound was active against representative HIV-2 and SIV strains. Compound was well tolerated after i.v. or s.c. administration and showed a good pharmacokinetic profile in animals. Currently being evaluated in a phase I/II trial in HIV-infected adults, T-1249 has received fast track designation from the FDA.

SOURCES – Roche; Trimeris.

REFERENCES

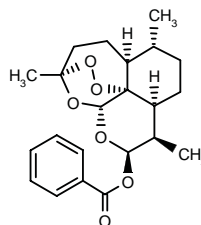
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2. Lambert, D.M. et al. *HIV-1 isolates from patients treated with T-20 are sensitive to the second generation fusion inhibitor T1249*. Antivir Ther 1999, 4(Suppl. 1): Abstr 10.
3. Venetta, T. et al. *Comparative pharmacokinetics of T-1249, a synthetic hybrid peptide inhibitor of HIV-1, SIV, and HIV-2 fusion*. 7th Eur Conf Clin Aspects Treat HIV Infect (Oct 23-27, Lisbon) 1999, Abstr 319.
4. *New, second-generation HIV fusion inhibitor from Trimeris to be evaluated clinically*. DailyDrugNews.com (Daily Essentials) 1999, April 20.
5. *Roche to develop and market Trimeris's HIV fusion inhibitors*. DailyDrugNews.com (Daily Essentials) 1999, July 13.
6. *Second HIV fusion inhibitor developed at Trimeris given fast track designation*. DailyDrugNews.com (Daily Essentials) 1999, May 17.
7. *Trimeris and Roche advance HIV fusion inhibitors in clinical testing*. DailyDrugNews.com (Daily Essentials) 2000, Feb 1.
8. *Trimeris begins phase I trial of second fusion inhibitor*. DailyDrugNews.com (Daily Essentials) 1999, July 7.

TREATMENT OF PROTOZOAL DISEASES

285349

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*R*,12*S*,12*aR*)-10-(Benzoyloxy)-3,6,9-trimethylperhydro-3,12-epoxypyrano[4,3-*j*]-1,2-benzodioxepine

10 β -Benzoyloxy-10-deoxoartemisinin



C22 H28 O6; Mol wt: 388.4572

ACTION – Antiparasitic agent, an artemisinin derivative reported to be particularly useful for the treatment of malaria, neosporosis and coccidiosis. Compound was more active than artemisinin when tested against *Neospora canium* and *Eimeria tenella* in cell culture *in vitro* and exhibited potent activity against both chloroquine-sensitive (D6) and -resistant (W2) strains of *Plasmodium falciparum*, giving IC₉₀ values of 0.03 and 0.21 ng/ml, respectively.

SOURCE – Hong Kong University of Science and Technology, Kowloon, Hong Kong (CN).

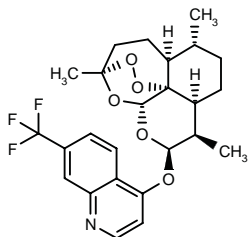
REFERENCES

1. Haynes, R.K. et al. (Hong Kong University of Science and Technology) *Artemisinin derivs. as anti-infective agent*. EP 0974594.

285350

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*R*,12*R*,12*aR*)-10-[7-(Trifluoromethyl)quinolin-4-yloxy]-3,6,9-trimethylperhydro-3,12-epoxypyran[4,3-*j*]-1,2-benzodioxepine

10β-(7'-Trifluoromethylquinolin-4-yloxy)-10-deoxy-artemisinin



C25 H28 F3 N O5; Mol wt: 479.4922

ACTION – Antiparasitic agent particularly effective in the treatment of malaria, neosporosis and coccidiosis, a derivative of artemisinin that was found to be active against *Neospora canium* and *Eimeria tenella* in cell culture *in vitro* and exhibited potent activity *in vitro* against both chloroquine-sensitive (D6) and -resistant (W2) strains of *Plasmodium falciparum*, giving IC₉₀ values of 0.93 and 0.81 ng/ml, respectively.

SOURCE – Hong Kong University of Science and Technology, Kowloon, Hong Kong (CN).

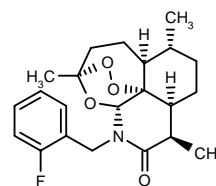
REFERENCES

1. Haynes, R.K. et al. (Hong Kong University of Science and Technology) *Artemisinin derivs.* EP 0974354.

285351

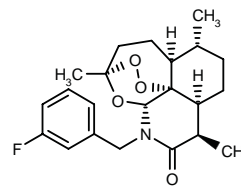
(3*R*,5*aS*,6*R*,8*aS*,9*R*,12*R*,12*aR*)-3,12-Epoxy-11-(2-fluorobenzyl)-3,6,9-trimethylperhydro-1,2-dioxepino[4,3-*j*]-isoquinolin-10-one

N-(2-Fluorobenzyl)-11-azaartemisinin



C22 H28 F N O4; Mol wt: 389.4642

ACTION – Antiparasitic agent particularly useful for the treatment of malaria, neosporosis and coccidiosis, with potent activity *in vitro* against both chloroquine-sensitive (D6) and -resistant (W2) strains of *Plasmodium falciparum*, giving IC₉₀ values of 0.99 and 0.975 ng/ml, respectively. Another compound from this series of artemisinin derivatives is:



285352: C22 H28 F N O4

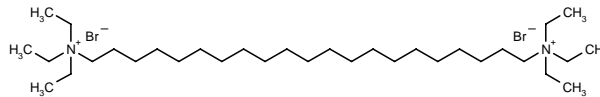
SOURCE – Hong Kong University of Science and Technology, Kowloon, Hong Kong (CN).

REFERENCES

1. Haynes, R.K. and Lam, W.-L. (Hong Kong University of Science and Technology) *Artemisinin derivs. as antiparasitic agents*. EP 0974593.

285378

*N*¹,*N*¹,*N*¹,*N*²¹,*N*²¹,*N*²¹-Hexaethylhenicosane-1,21-diammonium dibromide



C33 H72 Br2 N2; Mol wt: 656.7538

ACTION – Antimalarial agent with strong *in vitro* activity against *Plasmodium falciparum* (IC₅₀ = 3 pM) and low cytotoxicity against mammalian macrophages and lymphoblastoid cells. Compound appeared to be specific for the choline carrier of infected erythrocytes compared to other cholinergic systems such as high-affinity choline transport in synaptosomes. It is reported to exert potent antimalarial activity *in vivo* in mouse and monkey models.

SOURCE – CNRS.

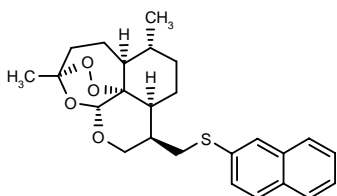
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- Calas, M. et al. Antimalarial activity of compounds interfering with *Plasmodium falciparum* phospholipid metabolism: Comparison between mono- and bisquaternary ammonium salts. *J Med Chem* 2000, 43(3): 505.

285479

(3*R*,5*aS*,6*R*,8*aS*,9*R*,12*R*,12*aR*)-3,6-Dimethyl-9-(2-naphthylsulfanyl)perhydro-3,12-epoxypyran[4,3-*j*]-1,2-benzodioxepine

9-Demethyl-10-deoxo-9-(2-naphthylsulfanylmethyl)-artemisinin



C₂₅ H₃₀ O₄ S; Mol wt: 426.5740

ACTION – Antiparasitic agent reported to be particularly effective in the treatment of malaria, neosporosis and coccidiosis, a derivative of artemisinin that exhibited potent activity against both chloroquine-sensitive (D6) and -resistant (W2) strains of *Plasmodium falciparum*, giving IC₉₀ values of 2.75 and 8.82 ng/ml, respectively.

SOURCE – Hong Kong University of Science and Technology, Kowloon, Hong Kong (CN).

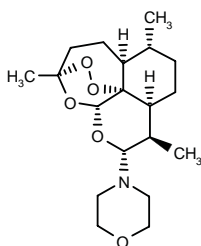
REFERENCES

- Haynes, R.K. et al. (Hong Kong University of Science and Technology) *Antiparasitic artemisinin derivs. (endoperoxides)*. WO 0004025.

285558

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*R*,12*R*,12*aR*)-10-(Morpholin-4-yl)-3,6,9-trimethylperhydro-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepine

10-Deoxo-10(*R*)-(morpholin-4-yl)artemisinin



C₁₉ H₃₁ N O₅; Mol wt: 353.4559

ACTION – Antiparasitic agent particularly effective in the treatment of malaria, neosporosis and coccidiosis, a derivative of artemisinin that displayed some activity against *Neospora canium* and *Eimeria tenella* in cell culture *in vitro*, as well as potent activity against both chloroquine-sensitive (D6) and -resistant (W2) strains of *Plasmodium falciparum*, giving IC₉₀ values of 0.35 and 0.17 ng/ml, respectively.

SOURCE – Hong Kong University of Science and Technology, Kowloon, Hong Kong (CN).

REFERENCES

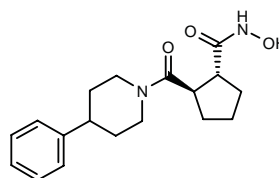
- Haynes, R.K. et al. (Hong Kong University of Science and Technology) *Antiparasitic artemisinin derivs. (endoperoxides)*. WO 0004024.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

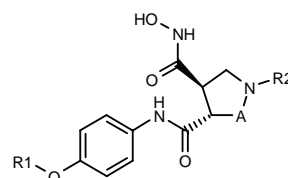
284855

trans-2-(4-Phenylpiperidin-1-ylcarbonyl)cyclopentane-carboxylic acid

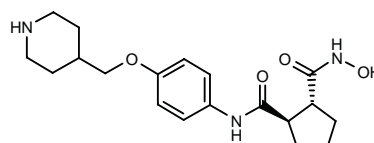


C₁₈ H₂₄ N₂ O₃; Mol wt: 316.3986

ACTION – An inhibitor of matrix metalloproteinases (MMPs) including aggrecanase and tumor necrosis factor convertase (TNF-C), and of the production of TNF, with potential in the treatment of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, multiple sclerosis, psoriasis, fever, cachexia, shock, graft-versus-host reaction, autoimmune diseases and HIV infection. Other specifically claimed compounds from this series of cyclic hydroxamic acid derivatives include the following:



Compound	R1	R2	A	Formula
284860	4-Pip	i-BuOCO	-(CH ₂) ₂ -	C ₂₃ H ₃₄ N ₄ O ₆
284863	2-Me-4-quinoliny-CH ₂	4-THP-OCO	-(CH ₂) ₂ -	C ₃₀ H ₃₄ N ₄ O ₇
284865	2-Me-4-quinoliny-CH ₂	COPh	-(CH ₂) ₂ -	C ₃₁ H ₃₀ N ₄ O ₅
284867	2,6-(Cl)2-4-Pyr-CH ₂	H	-CH ₂ -	C ₁₈ H ₁₈ Cl ₂ N ₄ O ₄



284856: C₁₉ H₂₇ N₃ O₄

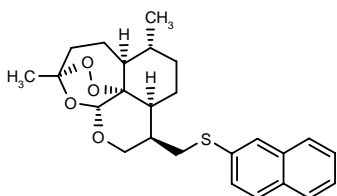
REFERENCES

- Calas, M. et al. Antimalarial activity of compounds interfering with *Plasmodium falciparum* phospholipid metabolism: Comparison between mono- and bisquaternary ammonium salts. *J Med Chem* 2000, 43(3): 505.

285479

(3*R*,5*aS*,6*R*,8*aS*,9*R*,12*R*,12*aR*)-3,6-Dimethyl-9-(2-naphthylsulfanyl)perhydro-3,12-epoxypyran[4,3-*J*]-1,2-benzodioxepine

9-Demethyl-10-deoxo-9-(2-naphthylsulfanylmethyl)-artemisinin



C₂₅ H₃₀ O₄ S; Mol wt: 426.5740

ACTION – Antiparasitic agent reported to be particularly effective in the treatment of malaria, neosporosis and coccidiosis, a derivative of artemisinin that exhibited potent activity against both chloroquine-sensitive (D6) and -resistant (W2) strains of *Plasmodium falciparum*, giving IC₉₀ values of 2.75 and 8.82 ng/ml, respectively.

SOURCE – Hong Kong University of Science and Technology, Kowloon, Hong Kong (CN).

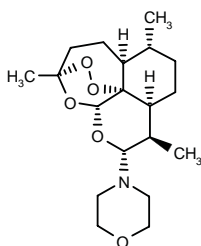
REFERENCES

- Haynes, R.K. et al. (Hong Kong University of Science and Technology) *Antiparasitic artemisinin derivs. (endoperoxides)*. WO 0004025.

285558

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*R*,12*R*,12*aR*)-10-(Morpholin-4-yl)-3,6,9-trimethylperhydro-3,12-epoxy-12*H*-pyrano[4,3-*J*]-1,2-benzodioxepine

10-Deoxo-10(*R*)-(morpholin-4-yl)artemisinin



C₁₉ H₃₁ N O₅; Mol wt: 353.4559

ACTION – Antiparasitic agent particularly effective in the treatment of malaria, neosporosis and coccidiosis, a derivative of artemisinin that displayed some activity against *Neospora canium* and *Eimeria tenella* in cell culture *in vitro*, as well as potent activity against both chloroquine-sensitive (D6) and -resistant (W2) strains of *Plasmodium falciparum*, giving IC₉₀ values of 0.35 and 0.17 ng/ml, respectively.

SOURCE – Hong Kong University of Science and Technology, Kowloon, Hong Kong (CN).

REFERENCES

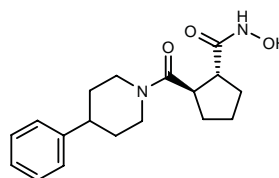
- Haynes, R.K. et al. (Hong Kong University of Science and Technology) *Antiparasitic artemisinin derivs. (endoperoxides)*. WO 0004024.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

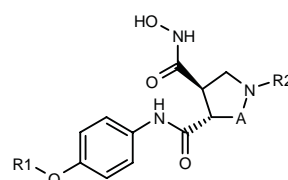
284855

trans-2-(4-Phenylpiperidin-1-ylcarbonyl)cyclopentane-carboxydroxamic acid

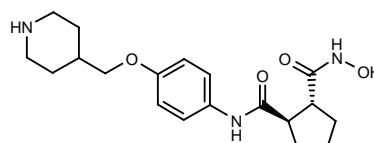


C₁₈ H₂₄ N₂ O₃; Mol wt: 316.3986

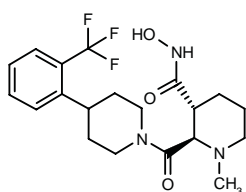
ACTION – An inhibitor of matrix metalloproteinases (MMPs) including aggrecanase and tumor necrosis factor convertase (TNF-C), and of the production of TNF, with potential in the treatment of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, multiple sclerosis, psoriasis, fever, cachexia, shock, graft-versus-host reaction, autoimmune diseases and HIV infection. Other specifically claimed compounds from this series of cyclic hydroxamic acid derivatives include the following:



Compound	R1	R2	A	Formula
284860	4-Pip	i-BuOCO	-(CH ₂) ₂ -	C ₂₃ H ₃₄ N ₄ O ₆
284863	2-Me-4-quinoliny-CH ₂	4-THP-OCO	-(CH ₂) ₂ -	C ₃₀ H ₃₄ N ₄ O ₇
284865	2-Me-4-quinoliny-CH ₂	COPh	-(CH ₂) ₂ -	C ₃₁ H ₃₀ N ₄ O ₅
284867	2,6-(Cl)2-4-Pyr-CH ₂	H	-CH ₂ -	C ₁₈ H ₁₈ Cl ₂ N ₄ O ₄



284856: C₁₉ H₂₇ N₃ O₄



284869: C20 H26 F3 N3 O3

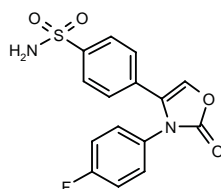
SOURCE – DuPont Pharmaceuticals.

REFERENCES

- Xue, C.-B. et al. (DuPont Pharmaceuticals Co.) *Cyclic hydroxamic acids as metalloproteinase inhibitors*. WO 9965867.

284942

4-[3-(4-Fluorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]-benzenesulfonamide



C15 H11 F N2 O4 S; Mol wt: 334.3259

ACTION – Antiinflammatory agent, a potent cyclooxygenase type 2 (COX-2) inhibitor (IC_{50} = 1.5 μ M) with 9-fold selectivity over COX-1 (IC_{50} = 13.2 μ M). Compound exhibited excellent oral activity in acute and chronic assays of inflammation, fever and pain in rats including carrageenan-induced paw edema (ED_{50} = 2.0 mg/kg), adjuvant-induced arthritis (ED_{50} = 0.6 mg/kg), carrageenan-induced air pouch inflammation (ED_{35} = 0.4 mg/kg), yeast-induced pyresis (ED_{50} = 2.4 mg/kg) and carrageenan-induced hyperalgesia (ED_{50} = 3.9 mg/kg). It was devoid of gastrointestinal toxicity in rats after a 4-day oral treatment at 100 mg/kg/day. Selected from a series of 3,4-diaryloxazolones for further preclinical evaluation.

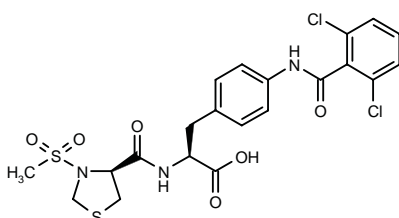
SOURCE – Almirall Prodesfarma.

REFERENCES

- Puig Duran, C. et al. (Almirall Prodesfarma, SA) *2-(3H)-Oxazolone derivs. and their use as COX-2 inhibitors*. EP 0888316, ES 2125161, WO 9734882.
- Puig, C. et al. *Synthesis and biological evaluation of 3,4-diaryloxazolones: A new class of orally active cyclooxygenase-2 inhibitors*. J Med Chem 2000, 43(2): 214.

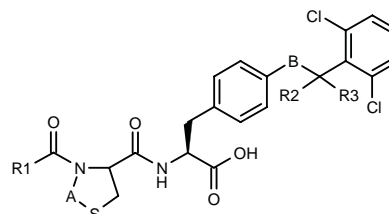
284948

N-[3-(Methylsulfonyl)thiazolidin-4(S)-ylcarbonyl]-4-(2,6-dichlorobenzamido)-L-phenylalanine



C21 H21 Cl2 N3 O6 S2; Mol wt: 546.4499

ACTION – Integrin antagonist claimed for use in the treatment or prevention of $\alpha_4\beta_1$ adhesion-mediated conditions such as rheumatoid arthritis, psoriasis, asthma, allergy, allograft rejection, atherosclerosis and ulcerative colitis. *In vitro*, compound was shown to inhibit $\alpha_4\beta_1$ binding to VCAM-1 or CS-1, as demonstrated in the Jurkat-endothelial cell (IC_{50} = 0.25 μ M or less) and Jurkat-CS-1 assays (IC_{50} = 0.05 μ M or less). In addition, it exhibited *in vivo* activity in a dextran pleurisy model in mice, giving > 40% inhibition of eosinophil infiltration into the pleural cavity at 50 mg/kg x 2 i.v. Other representative compounds include the following:



Compound	R1	R2	R3	A	B	Formula
284949	CH ₂ CH ₂ CO ₂ H	-O-	-CH ₂ -	NH		C ₂₄ H ₂₃ Cl ₂ N ₃ O ₇ S
284950	OE _t	-O-	-CH ₂ -	NH		C ₂₃ H ₂₃ Cl ₂ N ₃ O ₆ S
285199	4-morpholinyl-CH ₂ CH ₂ O	H	H	-CH ₂ -	O	C ₂₇ H ₃₁ Cl ₂ N ₃ O ₇ S
285200	CH ₂ CH ₂ CO ₂ H	-O-	-(CH ₂) ₂ -	NH		C ₂₅ H ₂₆ Cl ₂ N ₃ O ₇ S

SOURCES – Pharmacia; Tanabe Seiyaku.

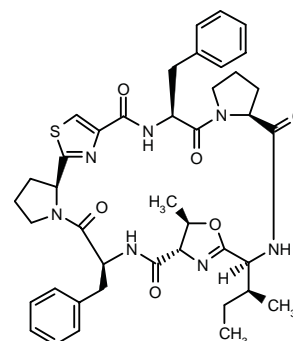
REFERENCES

- Blinn, J.R. et al. (Pharmacia & Upjohn Co.; Tanabe Seiyaku Co., Ltd.) *Inhibitors of $\alpha_4\beta_1$ mediated cell adhesion*. WO 9967230.

284979

trans,trans-(6*S*,12*aS*,18*S*,21*S*,22*R*,25*S*,27*aS*)-6,18-Dibenzyl-22-methyl-25-[1(*S*)-methylpropyl]-2,3,5,6,7,8,12*a*,13,14,15,17,18,19,20,21,22,25,26,27,27*a*-icosahydro-1*H*-9,12:21,24-dinitrilodipyrrolo[2,1-*f*:2',1'-*p*]-[1,14,4,7,10,17,20]oxathiapentaazacyclotricosine-5,8,17,20,27-pentaone

trans,trans-Ceratospongamide



C41 H49 N7 O6 S; Mol wt: 767.9471

White amorphous solid, $[\alpha]_D$ -39.2° (c 0.52, CHCl₃).

ACTION – Phospholipase A₂ inhibitor extracted from the Indonesian red alga *Ceratodictyon spongiosum* containing the symbiotic sponge *Sigmatocia symbiotica*. Compound was able to strongly inhibit IL-1β-induced PLA₂ secretion by hepatocellular carcinoma HepG2 cells with an IC₅₀ of 32 nM and to reduce reporter gene expression in reporter-transfected HepG2 cells stimulated with IL-1β (90% reduction at 50 ng/ml). Compound showed moderate potency in the brine shrimp toxicity assay (LD₅₀ = 13-19 μM). Potentially useful for the treatment of inflammatory diseases such as arthritis and sepsis.

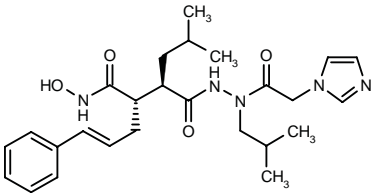
SOURCES – University of California, Santa Barbara, Santa Barbara, CA (US); Oregon State University, Corvallis, OR (US).

REFERENCES

1. Tong Tan, L. et al. *cis,cis- And trans,trans-ceratospongamide, new bioactive cyclic heptapeptides from the Indonesian red alga Ceratodictyon spongiosum and symbiotic sponge Sigmatocia symbiotica*. J Org Chem 2000, 65(2): 419.

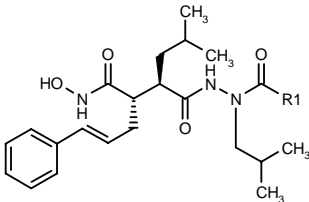
285001

2(S)-[1(R)-[3-[2-(1-Imidazolyl)acetyl]-3-isobutylcarbazoyl]-3-methylbutyl]-5-phenyl-4(E)-pentenohydroxamic acid



C26 H37 N5 O4; Mol wt: 483.6093

ACTION – Agent for the treatment of inflammatory and autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis and osteoarthritis, respiratory diseases such as asthma and chronic obstructive pulmonary disease, cancer, cachexia, cardiovascular diseases such as congestive heart failure, as well as fever, hemorrhage and sepsis, an inhibitor of the release of TNF-α, as demonstrated in lipopolysaccharide-stimulated THP-1 cells (IC₅₀ = 201 nM). Other specifically claimed compounds from this series of hydrazine derivatives include the following:



Compound	R1	Formula
285002	(R)-CH(Me)NH2	C ₂₄ H ₃₆ N ₄ O ₄
285003	CH(OH)Me	C ₂₄ H ₃₇ N ₃ O ₅
285005	4-Pip	C ₂₇ H ₄₂ N ₄ O ₄

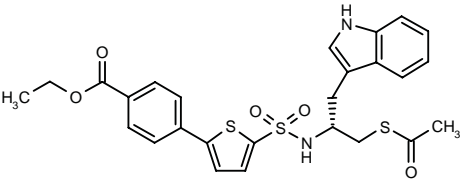
SOURCE – Roche.

REFERENCES

1. Broadhurst, M.J. et al. (F. Hoffmann-La Roche AG) *Hydrazine derivs*. WO 0000465.

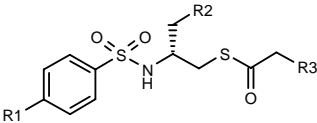
285157

4-[5-[N-[2-(Acetylsulfanyl)-1(R)-(1H-indol-3-ylmethyl)-ethyl]sulfamoyl]thien-2-yl]benzoic acid ethyl ester

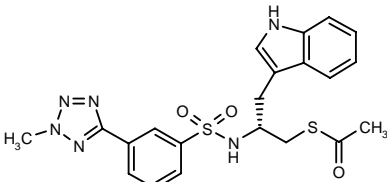


C26 H26 N2 O5 S3; Mol wt: 542.6984

ACTION – An inhibitor of the production of TNF-α, as demonstrated in lipopolysaccharide (LPS)-stimulated human monocytic THP-1 cells (IC₅₀ = 0.3 μM), with potential in the treatment of autoimmune diseases such as chronic rheumatoid arthritis, Crohn's disease, myasthenia gravis, systemic lupus erythematosus, asthma, type I diabetes and psoriasis. A representative compound from a series of sulfonamide derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
285159	OPh	3-indolyl	H	C ₂₅ H ₂₄ N ₂ O ₄ S ₂
285160	OPh	3-indolyl	Me	C ₂₆ H ₂₆ N ₂ O ₄ S ₂
285161	2-Ph-5-tetrazolyl	3-indolyl	H	C ₂₆ H ₂₄ N ₆ O ₃ S ₂
285162	1-imidazolyl	3-indolyl	H	C ₂₂ H ₂₂ N ₄ O ₃ S ₂
285163	4-Bu-Ph	3-indolyl	H	C ₂₉ H ₃₂ N ₂ O ₃ S ₂
285165	2-Me-5-tetrazolyl	3-indolyl	H	C ₂₁ H ₂₂ N ₆ O ₃ S ₂
285167	H	4-(t-BuO)-Ph	H	C ₂₁ H ₂₇ NO ₄ S ₂



285166: C21 H22 N6 O3 S2

SOURCE – Shionogi.

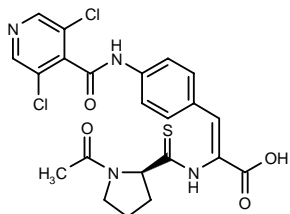
REFERENCES

1. Watanabe, F. et al. (Shionogi & Co. Ltd.) *Sulfonamide derivs. and TNFα production inhibitors containing them*. JP 1999343279.

285164

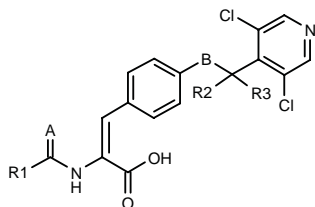
2-[1-Acetylpyrrolidin-2(*R*)-ylcarbothioamido]-3-[4-(3,5-dichloropyridin-4-ylcarboxamido)phenyl]-2(*Z*)-propenoic acid

N-Acetyl-D-thiopropyl-4-(3,5-dichloropyridin-4-ylcarbox-amido)-(Z)-didehydrophenylalanine



C₂₂ H₂₀ Cl₂ N₄ O₄ S; Mol wt: 507.3960

ACTION – Potent and selective α_4 integrin inhibitor that inhibits $\alpha_4\beta_1$ and/or $\alpha_4\beta_7$ integrins at concentrations with little or no inhibitory activity against α integrins of other subgroups. Potentially useful in the treatment of immune and inflammatory disorders, particularly rheumatoid arthritis, vasculitis, multiple sclerosis, allograft rejection, diabetes, psoriasis, dermatitis, asthma and inflammatory bowel disease. Other specifically claimed cinnamic acid derivatives are:



Compound	R1	R2	R3	A	B	Isomer	Formula
285168	(<i>R</i>)-1-Ac-2-pyrrolidinyl	-O-		S	NH	E	C ₂₂ H ₂₀ Cl ₂ N ₄ O ₄ S
285169	<i>t</i> -Bu	-O-		O	NH	Z	C ₂₀ H ₁₉ Cl ₂ N ₃ O ₄
285171	<i>t</i> -Bu	-O-		O	NH	E	C ₂₀ H ₁₉ Cl ₂ N ₃ O ₄
285175	2-Cl-3-Pyr	-O-		O	NH	Z	C ₂₁ H ₁₃ Cl ₃ N ₄ O ₄
285177	2,6-(MeO)2-Ph	H	H	O	O	Z	C ₂₄ H ₂₀ Cl ₂ N ₂ O ₆
285179	2-Cl-3-Pyr	-O-		O	NH	E	C ₂₁ H ₁₃ Cl ₃ N ₄ O ₄

SOURCE – Celltech Group.

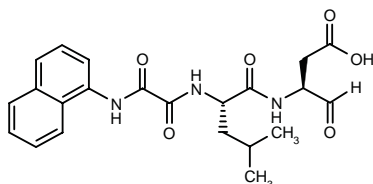
REFERENCES

1. Warrellow, G.J. et al. (Celltech Chiroscience plc) *Cinnamic acid derivs. as cell adhesion molecules*. WO 0001690.

285203

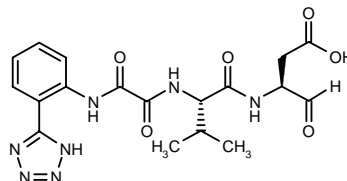
3(*S*)-[4-Methyl-2(*S*)-[2-(1-naphthylamino)-2-oxoacetamido]pentanamido]-4-oxobutyric acid

N-[2-(1-Naphthylamino)-2-oxoacetyl]-L-leucyl-L-aspart-1-al



C₂₂ H₂₅ N₃ O₆; Mol wt: 427.4545

ACTION – Agent for the treatment of inflammatory, autoimmune and neurodegenerative disorders, as well as for the prevention of ischemic injury and for the preservation of organs for transplantation, an inhibitor of IL-1 β -converting enzyme (ICE; IC₅₀ = 0.027 μ M) and related cysteine proteases such as CPP32 (IC₅₀ = 0.010 μ M), MCH-2 (IC₅₀ = 1.50 μ M), MCH-3 (IC₅₀ = 0.267 μ M) and MCH-5 (IC₅₀ = 0.179 μ M). Another compound from this series of C-terminal modified oxamyl dipeptides is:



285204: C₁₈ H₂₁ N₇ O₆

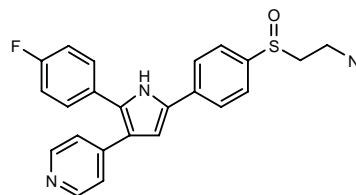
SOURCE – Idun.

REFERENCES

1. Karanewsky, D.S. and Ternansky, R.J. (Idun Pharmaceuticals, Inc.) *C-Terminal modified oxamyl dipeptides as inhibitors of the ICE/ced-3 family of cyteine proteases*. WO 0001666.

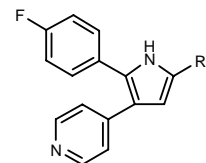
285288

4-[5-[4-(2-Azidoethylsulfinyl)phenyl]-2-(4-fluorophenyl)-1*H*-pyrrol-3-yl]pyridine



C₂₃ H₁₈ F N₅ O S; Mol wt: 431.4932

ACTION – An inhibitor of the production of inflammatory cytokines such as IL-1 β and TNF- α , a representative compound from a series of five-membered heteroaryl derivatives, wherein the following are also included:



Compound	R1	Formula
285289	4-[NO ₂ (CH ₂) ₃ SO ₂]-Ph	C ₂₄ H ₂₀ FN ₃ O ₄ S
285290	4-[N ₃ (CH ₂) ₃ SO]-Ph	C ₂₄ H ₂₀ FN ₃ OS
285291	1-[(EtO)2POCH ₂ CH ₂]-4-Pip	C ₂₆ H ₃₃ FN ₃ O ₃ P
285292	1-(NO ₂ CH ₂ CH ₂)-4-Pip	C ₂₂ H ₂₃ FN ₄ O ₂

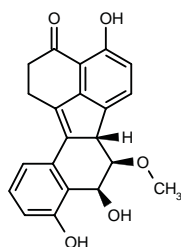
SOURCE – Sankyo.

REFERENCES

1. Kimura, T. et al. (Sankyo Co., Ltd.) *Five-membered heteroaryl cpds*. WO 0001688.

285321

(6a*R*,7*R*,8*S*)-4,8,9-Trihydroxy-7-methoxy-1,2,3,6a,7,8-hexahydrobenzo[*j*]fluoranthren-3-one



C21 H18 O5; Mol wt: 350.3682

ACTION – An inhibitor of cytokine production and tyrosine kinase activity isolated from the fermentation broth of the fungus *Cladosporium cf. cladosporioides* X20700 (CBS 100200). Compound inhibited anti-CD28-induced IL-2 release from Jurkat E6-1 cells and human T-cells (IC_{50} = 0.34 and 0.12 μ M, respectively), as well as lipopolysaccharide (LPS)-induced TNF- α release from human monocytes (IC_{50} = 0.42 μ M), and PHA- and LPS-induced TNF- α and IL-2 release from human whole blood at concentrations in the range 0.1-7 μ M. In addition, it inhibited abl tyrosine kinase activity (IC_{50} = 0.006 μ M). Potentially useful in the treatment of immunoinflammatory conditions such as rheumatoid arthritis, osteoarthritis, septic shock, psoriasis, inflammatory bowel disease, Crohn's disease, systemic lupus erythematosus, multiple sclerosis, diabetes and asthma, as well as cancer.

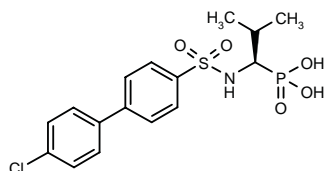
SOURCE – Xenova.

REFERENCES

1. Giuliani, R.M.S. et al. (Xenova Group plc) *Cytokine production and tyrosine kinase inhibitors*. WO 0002839.

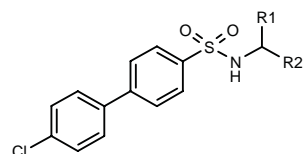
285474

1(*R*)-(4'-Chlorobiphenyl-4-yl)sulfonamido)-2-methylpropylphosphonic acid



C16 H19 Cl N O5 P S; Mol wt: 403.8211

ACTION – An inhibitor of matrix metalloproteinases (MMPs) such as human stromelysin (MMP-3; IC_{50} = 6 nM), human neutrophil collagenase (MMP-8; IC_{50} = 1 nM) and aggrecanase (IC_{50} = 0.6 μ M in rat chondrosarcoma cells), with potential in the treatment of osteoarthritis, acute and chronic arthritis, periodontal diseases, bone disorders, ulceration, atherosclerosis, restenosis, cancer, cachexia and septic shock. Other specifically claimed compounds from this series of phosphinic and phosphonic acid derivatives are:



Compound	R1	R2	Formula
285475	CH ₂ CH(OH)PO(OMe) ₂	4-CF ₃ -Ph	C ₂₄ H ₂₄ ClF ₃ NO ₆ PS
285476	PO ₃ H ₂	i-Bu	C ₁₇ H ₂₁ ClNO ₅ PS
285477	PO(OEt)OH	Ph	C ₂₁ H ₂₁ ClNO ₅ PS

SOURCE – Aventis Pharma.

REFERENCES

1. Schudok, M. et al. (Aventis Pharma Deutschland GmbH) *Phosphinous and phosphonic acid derivs. used as medicaments*. DE 19831980, WO 0004030.

ISIS-19493

284687

18-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-AGGCAGTGTCTGAGGTGG-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides; the cytidines in these terminal groups are 2'-O-methoxyethyl-5-methylcytidines

ACTION – Antisense phosphorothioate oligonucleotide targeted to nucleic acids encoding the human cell-surface TNF receptor TNFR1, with potential in the treatment of conditions associated with TNFR1 expression such as inflammatory disorders. Compound gave 96% inhibition of TNFR1 mRNA levels in transitional cell bladder carcinoma T-24 cells at a concentration of 150 nM. Other exemplified antisense oligonucleotides include the following:

18-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-AGACTCGGGCATAGAGAT-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides; the cytidines in these terminal groups are 2'-O-methoxyethyl-5-methylcytidines

ISIS-19465 [284688]

18-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-CTCAGGGCAGTGTGGCAG-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides; the cytidines in these terminal groups are 2'-O-methoxyethyl-5-methylcytidines

ISIS-19472 [284689]

18-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-GCAGGTCAGGCACGGTGG-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides; the cytidines in these terminal groups are 2'-O-methoxyethyl-5-methylcytidines

ISIS-19476 [284690]

18-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-AGCGGCAGCAGCAGGTCA-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides; the cytidines in these terminal groups are 2'-O-methoxyethyl-5-methylcytidines

ISIS-19478 [284691]

18-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-GACCCATTTCCTTCGGC-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides; the cytidines in these terminal groups are 2'-O-methoxyethyl-5-methylcytidines

ISIS-19496 [284692]

18-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-GCTTTTCTTACAGTTACT-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides; the cytidines in these terminal groups are 2'-O-methoxyethyl-5-methylcytidines

ISIS-19505 [284693]

18-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-CTCAGGGACGAACCAGGG-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides; the cytidines in these terminal groups are 2'-O-methoxyethyl-5-methylcytidines

ISIS-19536 [284694]

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Baker, B.F. and Cowser, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of TNFR1 expression*. WO 0000504.

R-125224

283395

Humanized IgG₁ anti-Fas monoclonal antibody

h-HFE7A

ACTION – Humanized IgG₁ anti-Fas monoclonal antibody (MAb) able to induce apoptosis in lymphocytes and in synovial cells from rheumatoid arthritis patients (25-30%), with an effect equivalent to the commercially available nonhumanized anti-Fas MAb CH-11. In the SCID-Hu RAG mouse model of rheumatoid arthritis prepared by grafting synovium, cartilage and bone of rheumatoid arthritis patients, compound induced a marked decrease in the number of inflammatory cells (70-90% compared to controls at 100 µg). Potentially useful for the treatment of rheumatoid arthritis.

SOURCE – Sankyo.

REFERENCES

1. Matsuno, H. et al. *Possibility of R-125224 (h-HFE7A), a novel humanized anti-Fas antibody, as therapeutic agent for chronic rheumatoid arthritis*. Proc Jpn Soc Immunol 1999, 29:188.

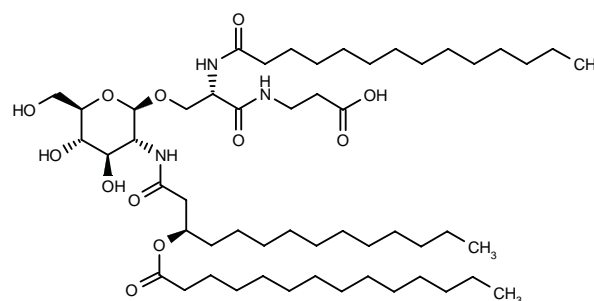
2. Matsuno, H. et al. *The effect of h-HFE7-A, a novel reshaping humanized anti-Fas monoclonal antibody, on SCID-Hu RAG model*. 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abstr 304.

3. Ohtsuki, M. et al. *Apoptosis inducing effect of R-125224 (h-HFE7A), a novel humanized anti-Fas antibody, in vitro*. Proc Jpn Soc Immunol 1999, 29: 196.

IMMUNOMODULATING AGENTS

285026

O-[2-Deoxy-2-[3(R)-(tetradecanoyloxy)tetradecanoyl-amino]-β-D-glucopyranosyl]-N-(tetradecanoyl)-L-seryl-β-alanine



C54 H101 N3 O12; Mol wt: 984.4009

Amorphous powder, $[\alpha]_D -5.2^\circ$ (c 0.34, CHCl₃).

ACTION – Synthetic vaccine immunoadjuvant, a lipid A analogue with high mitogenic activity in murine splenocytes at a concentration of 12.5 µM and low lethal toxicity in D-galactosamine-loaded mice.

SOURCE – University of Shizuoka, Shizuoka (JP).

REFERENCES

1. Ikeda, K. et al. *Lipid A and related compounds. XXXVII. Determination of favorable binding linkages of lipid A analog to antigen moiety for synthetic vaccines*. Chem Pharm Bull 2000, 48(1): 32.
2. Miyajima, K. et al. *Synthesis of TN and sialyl TN antigen-lipid analog conjugates for synthetic vaccines*. Chem Pharm Bull 1997, 45(9): 1544.

285052

L-Leucyl-L-leucyl-L-methionylglycyl-L-threonyl-L-leucylglycyl-L-isoleucyl-L-valyl-L-cysteinyl-L-prolyl-L-isoleucyl-L-cysteine

C59 H105 N13 O15 S3; Mol wt: 1332.7520

ACTION – Immunogenic peptide from the human papillomavirus (HPV) type 16 E7 protein that contains two overlapping class I HLA-A2-binding T-cell epitopes, for use in the preparation of vaccines for the treatment and prevention of HPV infection or HPV-associated disorders. Also disclosed are further immunogenic peptides derived from the same source, as well as nucleic acids encoding them and delivery systems therefor.

18-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-AGCGGCAGCAGCAGGTCA-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides; the cytidines in these terminal groups are 2'-O-methoxyethyl-5-methylcytidines

ISIS-19478 [284691]

18-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-GACCCATTTCCTTCGGC-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides; the cytidines in these terminal groups are 2'-O-methoxyethyl-5-methylcytidines

ISIS-19496 [284692]

18-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-GCTTTTCTTACAGTTACT-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides; the cytidines in these terminal groups are 2'-O-methoxyethyl-5-methylcytidines

ISIS-19505 [284693]

18-Mer antisense phosphorothioate oligonucleotide whose sequence is: 5'-CTCAGGGACGAACCAGGG-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides; the cytidines in these terminal groups are 2'-O-methoxyethyl-5-methylcytidines

ISIS-19536 [284694]

SOURCE – Isis Pharmaceuticals.

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1. Baker, B.F. and Cowser, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of TNFR1 expression*. WO 0000504.

R-125224

283395

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ACTION – Humanized IgG₁ anti-Fas monoclonal antibody (MAb) able to induce apoptosis in lymphocytes and in synovial cells from rheumatoid arthritis patients (25-30%), with an effect equivalent to the commercially available nonhumanized anti-Fas MAb CH-11. In the SCID-Hu RAG mouse model of rheumatoid arthritis prepared by grafting synovium, cartilage and bone of rheumatoid arthritis patients, compound induced a marked decrease in the number of inflammatory cells (70-90% compared to controls at 100 µg). Potentially useful for the treatment of rheumatoid arthritis.

SOURCE – Sankyo.

REFERENCES

1. Matsuno, H. et al. *Possibility of R-125224 (h-HFE7A), a novel humanized anti-Fas antibody, as therapeutic agent for chronic rheumatoid arthritis*. Proc Jpn Soc Immunol 1999, 29:188.

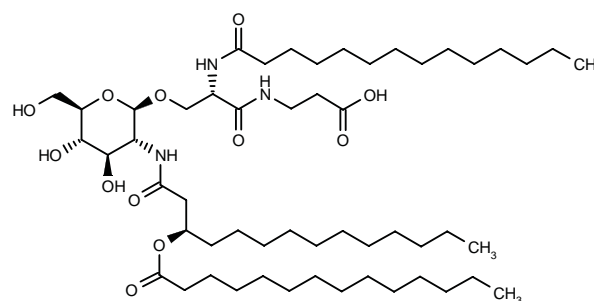
2. Matsuno, H. et al. *The effect of h-HFE7-A, a novel reshaping humanized anti-Fas monoclonal antibody, on SCID-Hu RAG model*. 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abstr 304.

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IMMUNOMODULATING AGENTS

285026

O-[2-Deoxy-2-[3(R)-(tetradecanoyloxy)tetradecanoyl-amino]-β-D-glucopyranosyl]-N-(tetradecanoyl)-L-seryl-β-alanine



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REFERENCES

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2. Miyajima, K. et al. *Synthesis of TN and sialyl TN antigen-lipid analog conjugates for synthetic vaccines*. Chem Pharm Bull 1997, 45(9): 1544.

285052

L-Leucyl-L-leucyl-L-methionylglycyl-L-threonyl-L-leucylglycyl-L-isoleucyl-L-valyl-L-cysteinyl-L-prolyl-L-isoleucyl-L-cysteine

C59 H105 N13 O15 S3; Mol wt: 1332.7520

ACTION – Immunogenic peptide from the human papillomavirus (HPV) type 16 E7 protein that contains two overlapping class I HLA-A2-binding T-cell epitopes, for use in the preparation of vaccines for the treatment and prevention of HPV infection or HPV-associated disorders. Also disclosed are further immunogenic peptides derived from the same source, as well as nucleic acids encoding them and delivery systems therefor.

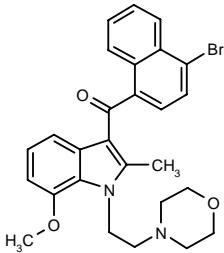
SOURCE – Zycos.

REFERENCES

1. Urban, R.G. et al. (Zycos Inc.) *Immunogenic peptides from the HPV E7 protein*. US 6013258.

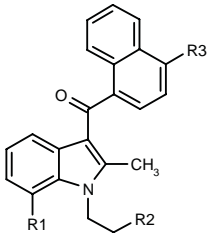
285089

1-(4-Bromonaphthalen-1-yl)-1-[7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl]methanone



C27 H27 Br N2 O3; Mol wt: 507.4253

ACTION – Immunomodulating agent, a selective cannabinoid CB₂ receptor agonist, as demonstrated in binding assays by K_i values for human CB₂ and CB₁ receptors expressed in CHO cells of 1.8 nM and > 1000 nM, respectively, and in functional assays by IC₅₀ values of 1 nM and 1 μM for inhibition of forskolin-stimulated adenylate cyclase activity in CHO cells expressing human CB₂ and CB₁ receptors, respectively. Other specifically claimed compounds from this series of indole derivatives include the following:



Compound	R1	R2	R3	Formula
285090	OMe	4-morpholinyl	F	C ₂₇ H ₂₇ FN ₂ O ₃
285091	OMe	4-morpholinyl	Cl	C ₂₇ H ₂₇ ClN ₂ O ₃
285092	OMe	Pr	Cl	C ₂₆ H ₂₆ ClNO ₂
285093	OMe	Pr	Br	C ₂₆ H ₂₆ BrNO ₂
285094	CF3	4-morpholinyl	H	C ₂₇ H ₂₅ F ₃ N ₂ O ₂
285095	CF3	4-morpholinyl	Br	C ₂₇ H ₂₄ BrF ₃ N ₂ O ₂
285096	F	4-morpholinyl	Br	C ₂₆ H ₂₄ BrFN ₂ O ₂
285097	F	Pr	Br	C ₂₅ H ₂₃ BrFNO
285098	Me	4-morpholinyl	Br	C ₂₇ H ₂₇ BrN ₂ O ₂

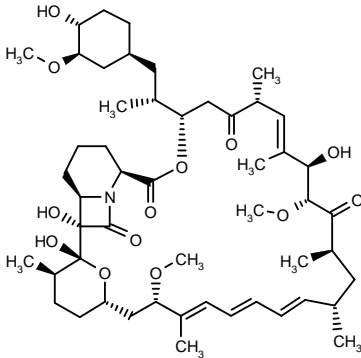
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Rinaldi, M. et al. (Sanofi-Synthélabo) *CB₂ receptor agonist cpds*. EP 0833818, FR 2735774, US 6013648, WO 9700860.

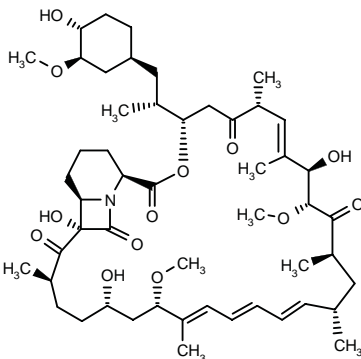
285225

(1*R*,2*S*,5*R*,9*S*,12*S*,15*R*,18*R*,19*R*,21*R*,23*S*,30*S*,32*S*,35*R*)-1,2,18-Trihydroxy-12-[2-[4(*R*)-hydroxy-3(*R*)-methoxy-1(*S*)-cyclohexyl]-1(*R*)-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-azatetracyclo[30.3.1.0^{2,5}.0^{4,9}]hexatriaconta-16,24,26,28-tetraene-3,10,14,20-tetraone



C51 H79 N O13; Mol wt: 914.1791

ACTION – Rapamycin (sirolimus) derivative reported to possess immunosuppressive, antifungal, antiproliferative and antiinflammatory activity. Antineoplastic activity was demonstrated *in vitro* against ovarian cancer A2780S, cisplatin-resistant ovarian cancer A2780DDP, epidermoid cancer A431, colon cancer SW620 and breast cancer SKBR3 and MDA-MB-435 cells (IC₅₀ = 8.756, 6.51, 20.46, 24.84, 7.029 and 27.28 μg/ml, respectively). Some antifungal activity was observed *in vitro* against *Candida strains*, with MIC values in the range of 8-64 μg/ml or greater. Another rapamycin derivative is:



285227: C51 H79 N O13

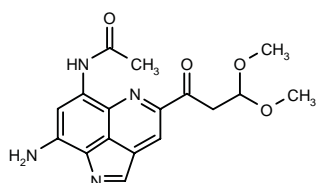
SOURCE – American Home Products.

REFERENCES

1. Zhu, T. and Lee, H.-K. (American Home Products Corp.) *Photocyclized rapamycin*. US 6015809.
2. Zhu, T. and Lee, H.-K. (American Home Products Corp.) *Photocyclized rapamycins*. WO 0009510.

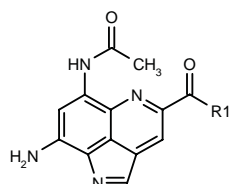
285226

N-[8-Amino-4-(3,3-dimethoxypropionyl)pyrrolo[4,3,2-*de*]-quinolin-6-yl]acetamide



C₁₇ H₁₈ N₄ O₄; Mol wt: 342.3532

ACTION – Immunosuppressive and antineoplastic agent shown to inhibit T-cell proliferation in a murine mixed lymphocyte reaction (IC₅₀ = 0.032 μM). *In vivo*, compound was active against a TNBS-induced delayed-type hypersensitivity reaction in mouse paw, giving 77% inhibition at 30 mg/kg i.p. versus 83% inhibition for ciclosporin at a dose of 30 mg/kg p.o. Other compounds within this series of LK6-A derivatives include the following:



Compound	R1	Formula
285228	(Z)-CH=CHNH ₂	C ₁₅ H ₁₃ N ₅ O ₂
285229	1,3-dioxolan-2-yl-CH ₂	C ₁₇ H ₁₈ N ₄ O ₄

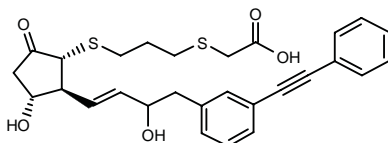
SOURCE – Kyowa Hakko.

REFERENCES

1. Akama, T. et al. (Kyowa Hakko Kogyo Co., Ltd.) *LK6-A derivs.* WO 0002879.

285393

16-[3-(2-Phenylethynyl)phenyl]-17,18,19,20-tetranor-3,7-dithiaprostaglandin E₂



C₂₈ H₃₀ O₅ S₂; Mol wt: 510.6720

ACTION – Agent for the treatment of immune disorders such as autoimmune diseases and organ transplant rejection, as well as asthma, osteodystrophy, neurodegenerative disorders, hepatic disorders, nephritis, hypertension, myocardial ischemia and sleep disorders, with selective affinity for prostanoid EP₄ receptors, as demonstrated in a binding assay by K_i values of 0.0003 and 0.23 μM, respectively, for murine EP₄ and EP_{3α} receptors cloned in CHO cells. A representative compound from a series of 3,7-dithiaprostanic acid derivatives.

SOURCE – Ono.

REFERENCES

1. Maruyama, T. and Ohuchida, S. (Ono Pharmaceutical Co., Ltd.) *3,7-Dithiaprostanic acid derivs., their preparation method, and agents containing them as active ingredient.* JP 2000001472.

ISIS-13280**282441**

20-Mer phosphorothioate oligonucleotide whose sequence is: 5'-GCCCAAGCTGGCATCCGTCA-3', in which the first twelve nucleotides flanking the 5'-end and the last nucleotide in position 20 are 2'-deoxynucleotides, nucleotides in positions 13, 14, 17 and 18 are 2'-methoxyethoxynucleotides and cytidines in positions 15, 16 and 19 are 2'-methoxyethoxy-5-methylcytidines

ACTION – Antisense oligonucleotide designed to hybridize to human ICAM-1 mRNA, proven to selectively inhibit tumor necrosis factor (TNF-α)-induced expression of ICAM-1 in human umbilical vein endothelial cells (HUVEC), giving 50.2 and 88.0% inhibition at 6.25 and 50 nM, respectively. Potentially useful in the treatment of allograft rejection, transplant-associated arteriosclerosis, graft-versus-host disease and for inhibiting viral dissemination. Other specifically claimed antisense oligonucleotides include the following:

20-Mer phosphorothioate oligonucleotide whose sequence is: 5'-GCCCAAGCTGGCATCCGTCA-3', in which the first twelve nucleotides flanking the 5'-end and the last nucleotide in position 20 are 2'-deoxynucleotides, nucleotides in positions 13, 14, 17 and 18 are 2'-fluoronucleotides and cytidines in positions 15, 16 and 19 are 2'-fluoro-5-methylcytidines

ISIS-12604 [282442]

20-Mer phosphorothioate oligonucleotide whose sequence is: 5'-GCCCAAGCTGGCATCCGTCA-3', in which the first twelve nucleotides flanking the 5'-end are 2'-deoxynucleotides, nucleotides in positions 13, 14, 17, 18 and 20 are 2'-methoxyethoxynucleotides and cytidines in positions 15, 16 and 19 are 2'-methoxyethoxy-5-methylcytidines

ISIS-14725 [282443]

20-Mer phosphorothioate oligonucleotide whose sequence is: 5'-GCCCAAGCTGGCATCGTCA-3', in which the first twelve nucleotides flanking the 5'-end are 2'-deoxynucleotides, cytidines in positions 2, 3, 4 and 8 are in addition 5-methylcytidines, nucleotides in positions 13, 14, 17, 18 and 20 are 2'-methoxyethoxynucleotides and cytidines in positions 15, 16 and 19 are 2'-methoxyethoxy-5-methylcytidines

ISIS-15839 [282444]

18-Mer phosphorothioate oligonucleotide whose sequence is: 5'-CCAAGCTGGCATCCGTCA-3', in which the first ten nucleotides flanking the 5'-end are 2'-deoxynucleotides, nucleotides in positions 11, 12, 15, 16 and 18 are 2'-methoxyethoxynucleotides and cytidines in positions 13, 14 and 17 are 2'-methoxyethoxy-5-methylcytidines

ISIS-16824 [282445]

16-Mer phosphorothioate oligonucleotide whose sequence is: 5'-AAGCTGGCATCCGTCA-3', in which the first eight nucleotides flanking the 5'-end are 2'-deoxynucleotides, nucleotides in positions 9, 10, 13, 14 and 16 are 2'-methoxyethoxynucleotides and cytidines in positions 11, 12 and 15 are 2'-methoxyethoxy-5-methylcytidines

ISIS-16823 [282446]

20-Mer phosphorothioate oligonucleotide whose sequence is: 5'-GTGCCCCAAGCTGGCATCCGT-3', in which the central nucleotides including positions 3-14 are 2'-deoxynucleotides, nucleotides in positions 1, 2, 15, 16, 19 and 20 are 2'-methoxyethoxynucleotides and cytidines in positions 17 and 18 are 2'-methoxyethoxy-5-methylcytidines

ISIS-16158 [282447]

22-Mer phosphorothioate oligonucleotide whose sequence is: 5'-AGCAGTGTGCCCCAAGCTGGCAT-3', in which the central nucleotides including positions 9-20 are 2'-deoxynucleotides, nucleotides in positions 1, 2, 4, 5, 6, 7, 8, 21 and 22 are 2'-methoxyethoxynucleotides and the cytidine in position 3 is 2'-methoxyethoxy-5-methylcytidine

ISIS-16159 [282448]

20-Mer phosphorothioate oligonucleotide whose sequence is: 5'-TCCCACAGCAGCTTGACGA-3', in which nucleotides in positions 1, 5, 7, 8, 10 and 11 are 2'-deoxynucleotides, cytidines in positions 2, 3, 4, 6 and 9 are 2'-deoxy-5-methylcytidines, nucleotides in positions 13, 14, 15, 17, 19 and 20 are 2'-methoxyethoxynucleotides and cytidines in positions 12, 16, 18 and 19 are 2'-methoxyethoxy-5-methylcytidines

ISIS-17481 [282449]

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Bennett, C.F. et al. (Isis Pharmaceuticals, Inc.) *Enhanced antisense modulation of ICAM-1*. WO 9954341.

MENINGOCOCCAL GROUP C CONJUGATE VACCINE

275881

Meningitis C conjugate vaccine

ACTION – Meningococcal group C conjugate vaccine.

INDICATION – Active immunization against type C meningitis.

PRESENTATION – Vials containing meningococcal group C oligosaccharide, 10 µg/0.5 ml, conjugated to *Corynebacterium diphtheriae* protein, as a suspension for i.m. injection.

PROPRIETARY NAME – Meningitec (GB).

SOURCE – Wyeth-Ayerst.

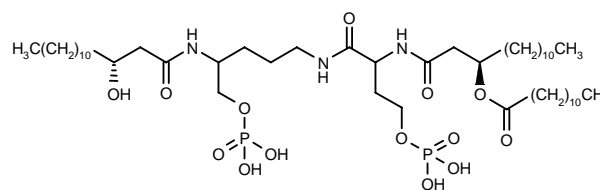
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1. U.K. launch of Meningitec coincides with initiation of national immunization program. DailyDrugNews.com (Daily Essentials) 1999, Nov 23.
2. U.K. regulatory filing for Wyeth Lederle Vaccines' meningococcal C conjugate vaccine. DailyDrugNews.com (Daily Essentials) 1999, May 7.
3. Wyeth is first to cross the finish line with meningococcal group C conjugate vaccine. DailyDrugNews.com (Daily Essentials) 1999, Oct 22.

OM-294DP

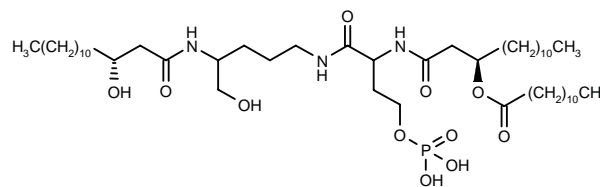
284959

2-[3(R)-(Dodecanoyloxy)tetradecanamido]-N-[4-[3(R)-hydroxytetradecanamido]-5-(phosphonoxy)pentyl]-4-(phosphonoxy)butyramide



C49 H97 N3 O14 P2; Mol wt: 1014.2600

ACTION – Immunomodulating agent with the ability to induce the production of nitric oxide (NO) in murine macrophages *in vitro* and to inhibit lipopolysaccharide (LPS)-stimulated TNF-α release in human alveolar macrophages (84% inhibition at 10 µg/ml). Significant antitumor activity was demonstrated in rats bearing PROb tumors at 1 mg/kg i.v. Compound can also be used as an adjuvant in association with suitable antigens for vaccination purposes, as demonstrated in several animal models. Another compound from this series of acyl pseudopeptides is:



OM-294MP [284960]: C49 H96 N3 O11 P

SOURCE – OM Pharma.

REFERENCES

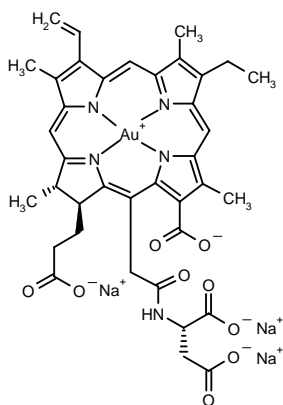
1. Bauer, J. and Martin, O.R. (OM Pharma SA) *Novel acyl pseudodipeptides, preparation method and pharmaceutical compsns. containing same*. WO 0000462.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

285246

Trisodium $[N-[2-[(2S,3S)-7\text{-carboxy-3-(2-carboxyethyl)-12-ethyl-2,8,13,18-tetramethyl-17-vinyl-2,3-dihydro-21H,23H-porphin-5-yl-}\kappa N^{21},\kappa N^{22},\kappa N^{23},\kappa N^{24}]acetyl]-L\text{-aspartato(6-)}]aurate(3-)]$



C38 H35 Au N5 Na3 O9; Mol wt: 971.6605

ACTION – Gold complex of a chlorin E₆ derivative for use as an X-ray therapeutic and diagnostic agent. Compound was shown to provide sharp images of solid tumors in mice and of atherosclerotic lesions in hypercholesterolemic rabbits following i.v. administration, and was proven effective in reducing the size of the solid tumors and atherosclerotic lesions in these animals.

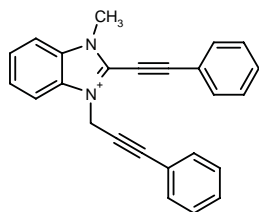
SOURCE – Meiji Seika.

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285459

3-Methyl-2-(2-phenylethynyl)-1-(3-phenyl-2-propynyl)-3H-benzimidazol-1-ium



C25 H19 N2; Mol wt: 347.4391

ACTION – DNA-cleaving antitumor agent, a representative compound from a series of aza derivatives of enediynes, enyne allenes and diallenes which undergo thermal reactions to produce diradical intermediates that induce DNA strand scission. Also reported to be potentially useful in the treatment of viral and bacterial infections.

SOURCE – University of Texas System, Austin, TX (US).

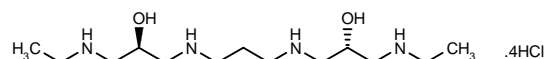
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ANTIMETABOLITES

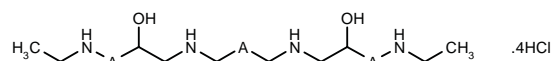
284935^{1,3}

3,7,11,15-Tetraazaheptadecane-5(*R*),13(*R*)-diol tetrahydrochloride



C13 H32 N4 O2 . 4HCl; Mol wt: 422.2654

ACTION – Antineoplastic agent, a polyamine analogue with *in vitro* cytotoxic activity against murine leukemia L1210 cells (IC₅₀ = 2.0-3.0 μM) and the ability to reduce putrescine and spermidine but not spermine pools, and moderately decrease levels of ornithine decarboxylase and S-adenosylmethionine decarboxylase in these cells, while being ineffective in upregulating spermidine/spermine N-acetyltransferase. No signs of neurotoxicity were observed in mice after treatment with compound at 217 mg/kg/day i.p. for 6 days. Further studies are in progress. Other related polyamine analogues include the following:



Compound	A	Isomer	Formula
284933 ^{1,3}	-(CH2)2-	6(S),15(S)	C ₁₆ H ₃₈ N ₄ O ₂ .4HCl
284934 ^{1,3}	-(CH2)2-	6(R),15(R)	C ₁₆ H ₃₈ N ₄ O ₂ .4HCl
284936 ^{1,3}	-CH2-	5(S),13(S)	C ₁₃ H ₃₂ N ₄ O ₂ .4HCl

SOURCE – University of Florida, Gainesville, FL (US).

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1. Bergeron, R.J. Jr. (University of Florida) *Hydroxy polyamines.* US 5962533.

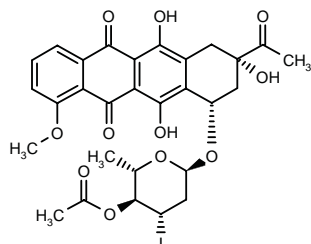
2. Bergeron, R.J. et al. *Metabolically programmed polyamine analogue antidiarrheals.* J Med Chem 1996, 39(13): 2461.

3. Bergeron, R.J. et al. *Synthesis and evaluation of hydroxylated polyamine analogues as antiproliferatives.* J Med Chem 2000, 43(2): 224.

ANTIBIOTICS AND ALKALOIDS

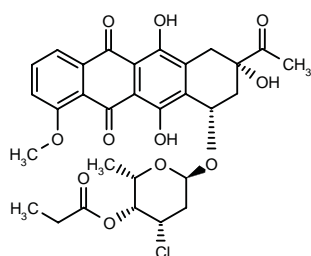
268485

7-*O*-(4'-*O*-Acetyl-2',3',6'-trideoxy-3'-iodo- α -L-mannopyranosyl)daunomycinone



C29 H29 I O11; Mol wt: 680.4371

ACTION – Antineoplastic antibiotic with broad-spectrum cytotoxic activity against normal and resistant cell lines including murine leukemia P388 and murine melanoma B16 (IC_{50} = 0.63 and 0.28 μ M), human colon carcinoma HT-29 (IC_{50} = 2.15 μ M), human non-small cell lung carcinoma NCI-H460 and A-549 (IC_{50} = 0.66 and 0.65 μ M, respectively), human ovarian carcinoma OVCAR-3 (IC_{50} = 1.73 μ M), human epidermoid carcinoma KB-3-1 (IC_{50} = 0.70 μ M) and its doxorubicin-resistant subline KB-A1 (IC_{50} = 1.78 μ M); doxorubicin showed superior potency against the above panel of cell lines (IC_{50} = 0.007-0.064 μ M) but was at least 8-fold less potent than compound against the resistant KB-A1 cell line (IC_{50} = 12.6 μ M). It induced cell cycle arrest, with accumulation of HT-29 cells in the G2+M phase, indicating that it acts as a DNA-intercalating agent. Another related compound is:



268486: C30 H31 Cl O11

SOURCE – Servier.

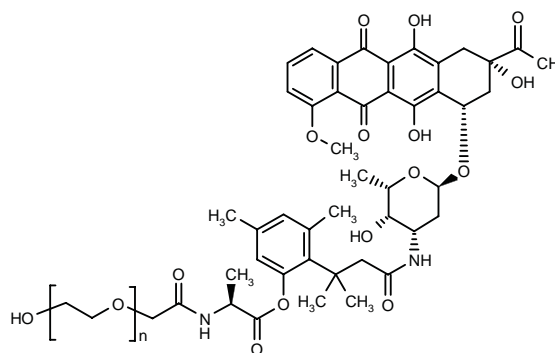
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2. Aliannis, N. et al. *Design, synthesis and biological activity of 7-O-(4-O-acetyl-3-iodo-2,3,6-trideoxy- α -L-arabino-hexopyranosyl)daunomycinone and 7-O-(3-chloro-2,3,6-trideoxy-4-O-propanoyl- α -L-lyxo-hexopyranosyl)daunomycinone*. Chem Pharm Bull 2000, 48(1): 150.

285377

N-[3,3-Dimethyl-3-[2-[*N*-[2-(polyethyleneglycol)acetyl]-L-alanyloxy]-4,6-dimethylphenyl]propionyl]daunorubicin



ACTION – Water-soluble polyethylene glycol prodrug of daunorubicin with *in vitro* cytotoxic activity against murine leukemia P388/0 cells lower than that of the parent compound (IC_{50} = 43 and 3 nM, respectively). Compound demonstrated prolonged stability in phosphate buffer at pH 7.4 and 37 degrees centigrade and a half-life of 1.9 h *in vitro* in rat plasma. It was more effective than daunorubicin *in vivo* in mice implanted with human ovarian adenocarcinoma SKOV3 xenografts.

SOURCE – Enzon.

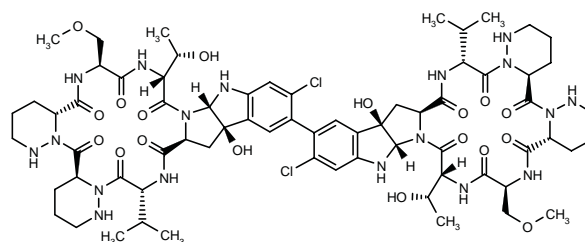
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CHLOPTOSIN

284989

22,22'-Bis[(4a*S*,10a*R*,13*S*,16*R*,18a*S*,23b*R*,24a*S*,27*R*)-21-chloro-23b-hydroxy-16-[1(*S*)-hydroxyethyl]-27-isopropyl-13-(methoxymethyl)-2,3,4,4a,8,9,10,10a,12,13,15,16,19,23b,24,24a,26,27-octadecahydro-18a*H*-dipyridazino[1'',6'':10',11':1'',6'':7',8'] [1,4,7,10,13,16]hexaazacyclooctadecino[2',1':5,1]pyrrolo[2,3-*b*]indole-5,11,14,17,25,28-hexanone]



C68 H94 Cl2 N18 O18; Mol wt: 1522.5050

ACTION – Antineoplastic antibiotic isolated from the culture broth of *Streptomyces* strain MK498-98F14 and proven able to induce apoptosis in apoptosis-resistant human pancreatic adenocarcinoma AsPC-1 cells (EC_{50} = 2.5 μ g/ml) and in apoptosis-sensitive human pancreatic adenocarcinoma BxPC-3, human fibrosarcoma HT1080 and human Jurkat T-cell leukemia cell lines (EC_{50} = 0.49, 0.07 and 0.20 μ g/ml, respectively). Compound inhibited the growth of AsPC-1, BxPC-3, HT1080 and Jurkat cells with IC_{50} values of 50, 12, 5.4 and 6.4 ng/ml, respectively, after 48-h treatment. Compound induced nuclear fragmentation after 24 h and internucleosomal DNA fragmentation after 18 h at 3-10 μ g/ml in AsPC-1 cells, and selectively inhibited RNA synthesis at 0.1-1 μ g/ml in these cells. Antibacterial activity was seen against Gram-positive strains including *Staphylococcus*, *Micrococcus* and *Bacillus* spp. (MIC = 0.025-1.56 μ g/ml) and it was effective against methicillin-resistant *Staphylococcus aureus* (MIC₅₀/MIC₉₀ = 0.78 μ g/ml), whereas it was not effective against Gram-negative microorganisms.

SOURCES – Keio University, Tokyo (JP); Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

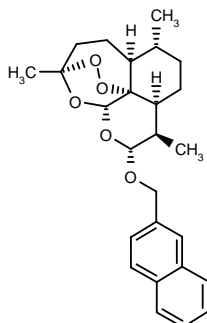
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DNA-INTERCALATING DRUGS

285569

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*R*,12*R*,12*aR*)-3,6,9-Trimethyl-10-(2-naphthylmethoxy)perhydro-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepine

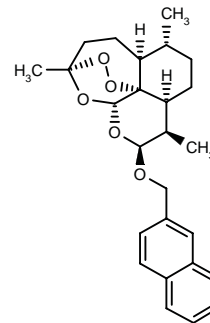
10-Deoxo-10(*R*)-(2-naphthylmethoxy)artemisinin



C26 H32 O5; Mol wt: 424.5338

ACTION – A representative compound from a series of antitumor agents comprising a ligand capable of binding to a nucleic acid and a trioxane-containing moiety capable of acting as a source of free radicals which chemically interact with a nucleic acid. Compound gave LD₅₀ values against the Rat 6 subclone of the immortalized F2 408 embryo cell line and c-H-ras oncogene-transformed Rat 6 (R6T24) cells of 0.14 and 0.12 μ M, respectively, on day 3 and of 0.037 and 0.02 μ M, respectively, on day 6. In addition, it exhibited cytotoxicity against human colon cancer SW480 and HT-29 and murine melanoma B16F10

cell lines, with LD₅₀ values of 200, 500 and 300 nM, respectively. Another compound from this series of trioxane derivatives is:



285570: C26 H32 O5

SOURCE – Hong Kong University of Science and Technology, Kowloon, Hong Kong (CN).

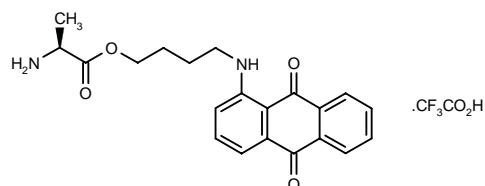
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NU:UB-73

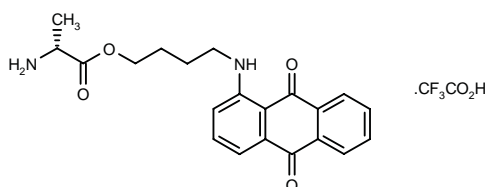
284954

L-Alanine 4-(9,10-dioxo-9,10-dihydroanthracen-1-ylamino)butyl ester trifluoroacetate



C21 H22 N2 O4 . C2 H F3 O2; Mol wt: 480.4367

ACTION – Antineoplastic and antiviral agent that acts by inhibiting topoisomerases, with selectivity for topoisomerases I and II β relative to topoisomerase II α . *In vitro*, compound was shown to be active against both doxorubicin-resistant and -sensitive CHO cell lines (IC_{50} = 54.0, 6.6 and 25.2 μ M, respectively, against CHO-K1, CHO-ADR-1 and CHO-ADR-r cell lines). Compound was also highly active against colon adenocarcinoma MAC15A both *in vitro* (IC_{50} = 2.6 μ M) and *in vivo* in mice bearing s.c. implanted tumors. It is also reported to be cytotoxic *in vitro* against lung NCI-H460, breast MCF-7 and CNS SF-268 tumor cell lines. Another compound from this series of anthracene derivatives is:



NU:UB-76 [284955]: C21 H22 N2 O4 . C2 H F3 O2

SOURCE – BTG.

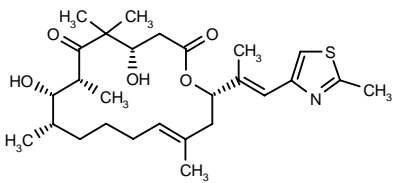
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ANTIMITOTIC DRUGS

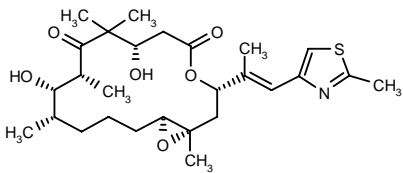
284702

4(*S*),8(*S*)-Dihydroxy-5,5,7(*R*),9(*S*),14-pentamethyl-16(*S*)-[(*E*)-1-methyl-2-(2-methylthiazol-4-yl)vinyl]oxacyclohexadec-13(*E*)-ene-2,6-dione

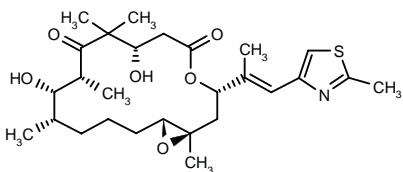


C27 H41 N O5 S; Mol wt: 491.6889

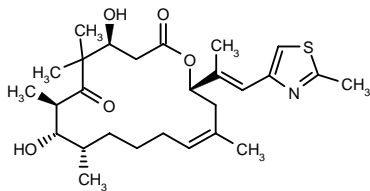
ACTION – Antineoplastic agent that interacts with tubulin by stabilizing formed microtubules. Compound is reported to be capable of influencing cell division in a phase-specific manner and is suitable for the treatment of malignant tumors such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant melanoma, and acute lymphocytic and myelocytic leukemia. It is also reported to be suited for antiangiogenesis therapy and for the treatment of chronic inflammatory diseases such as psoriasis and arthritis. Other exemplified compounds from this series of epothilone derivatives include the following:



284703: C27 H41 N O6 S



284705: C27 H41 N O6 S



284704: C27 H41 N O5 S

SOURCE – Schering AG.

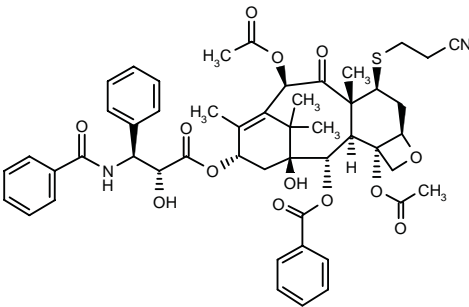
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285357

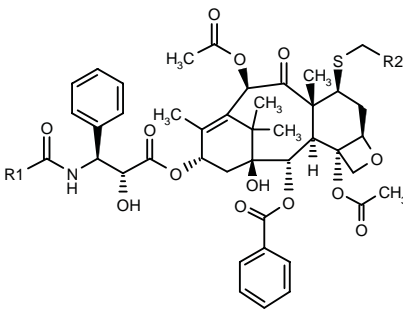
7β-(2-Cyanoethylsulfanyl)-7-deoxypaclitaxel

[2a*R*,4*S*,4a*S*,6*R*,9*S*(2'*R*,3'*S*),11*S*,12*S*,12a*R*,12b*S*]-6,12b-Diacetoxy-9-(3-benzamido-2-hydroxy-3-phenylpropionyl-oxy)-12-benzoyloxy-4-(2-cyanoethylsulfanyl)-11-hydroxy-4a,8,13,13-tetramethyl-7,11-methano-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-cyclodeca[3,4]benz-[1,2-*b*]oxet-5-one



C50 H54 N2 O13 S; Mol wt: 923.0436

ACTION – Antineoplastic agent with potent cytotoxicity against human colon carcinoma HCT-116 cells (IC₅₀ < 0.04 nM). Other compounds from this series of 7-sulfur substituted paclitaxel derivatives include the following:



Compound	R1	R2	Formula
285358	Ph	OMe	C ₄₉ H ₅₅ NO ₁₄ S
285359	Ph	H	C ₄₈ H ₅₃ NO ₁₃ S
285360	Ph	CH ₂ OH	C ₄₉ H ₅₅ NO ₁₄ S
285361	t-BuO	H	C ₄₈ H ₅₇ NO ₁₄ S

SOURCE – Bristol-Myers Squibb.

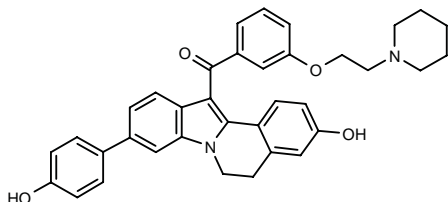
REFERENCES

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HORMONAL AGENTS

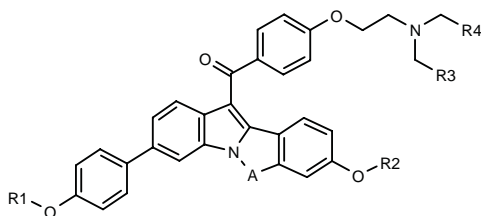
283962

1-[3-Hydroxy-9-(4-hydroxyphenyl)-5,6-dihydroindolo-[2,1-*a*]isoquinolin-12-yl]-1-[3-[2-(1-piperidinyl)ethoxy]phenyl]methanone



C36 H34 N2 O4; Mol wt: 558.6746

ACTION – Selective estrogen receptor modulator shown to inhibit 17 β -estradiol-stimulated proliferation of MCF-7 cells, being more potent than raloxifene. Compound was also shown to be more potent than raloxifene in stimulating the proliferation of estrogen receptor-expressing human osteosarcoma HOS cells and induced TGF- β production in HOS cells. Potentially useful for the treatment of estrogen deficiency-related disorders including breast cancer and osteoporosis. Other compounds from this series of 1-heteroindene derivatives include the following:



Compound	R1=R2	R3	R4	A	Formula
283963	H	-(CH2)3-	-(CH2)2-		C ₃₆ H ₃₄ N ₂ O ₄
283964	Me	H	H	-(CH2)2-	C ₃₅ H ₃₄ N ₂ O ₄
283965	Me	-(CH2)3-	-CO-		C ₃₇ H ₃₄ N ₂ O ₅

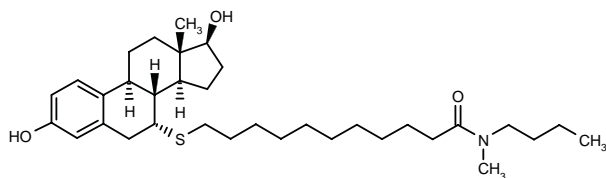
SOURCE – Senga.

REFERENCES

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285311

N-Butyl-11-[3,17 β -dihydroxyestra-1,3,5(10)-trien-7 α -ylsulfanyl]-*N*-methylundecanamide



C34 H55 N O3 S; Mol wt: 557.8785

ACTION – Antiestrogenic agent devoid of estrogenic activity, a potent estrogen receptor (ER) ligand (IC₅₀ = 9 nM for inhibition of [³H]-17 β -estradiol binding to both ER α and ER β receptors) with antagonist activity *in vitro* in a luciferase assay in human breast cancer MCF-7 cells (IC₅₀ = 3.5 nM) and *in vivo* in a 18-day-old rats, where it completely blocked the uterine weight gain induced by 17 β -estradiol. Potentially useful for the treatment of breast cancer.

SOURCE – Wyeth-Ayerst.

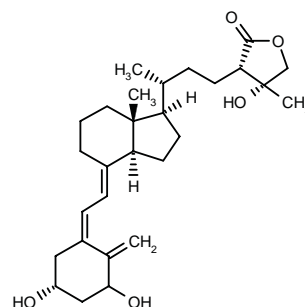
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2. Miller, C.P. et al. *Synthesis and estrogenic activities of novel 7-thiosubstituted estratriene derivatives*. Bioorg Med Chem Lett 2000, 10(2): 147.

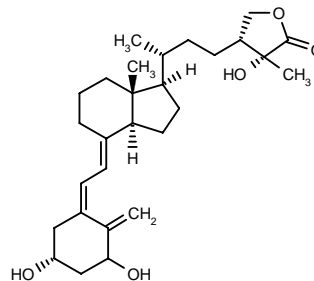
285395

3(*S*)-[(5*Z*,7*E*)-1,3 β -Dihydroxy-24-nor-9,10-secocholan-5,7,10(19)-trien-23-yl]-4(*R*)-hydroxy-4-methyltetrahydrofuran-2-one



C28 H42 O5; Mol wt: 458.6348

ACTION – Agent for the treatment of hyperproliferative diseases, osteoporosis and immunological disorders with a relative binding affinity (1,25-dihydroxyvitamin D₃ = 1.0) for the 1,25-dihydroxyvitamin D₃ receptor (VDR) of 0.03 and comparable potency to 1,25-dihydroxyvitamin D₃ in inducing differentiation of human myelogenous leukemia HL-60 cells (78% at 0.1 μ M for both). Another compound from this series of vitamin D derivatives is:



285396: C28 H42 O5

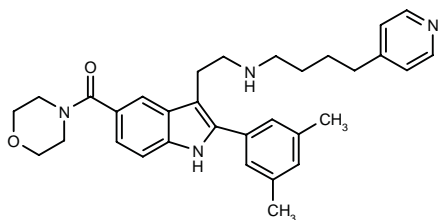
SOURCE – Nisshin Flour Milling.

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1. Tachibana, Y. (Nisshin Flour Milling Co., Ltd.) *Active vitamin D derivs*. JP 2000016987.

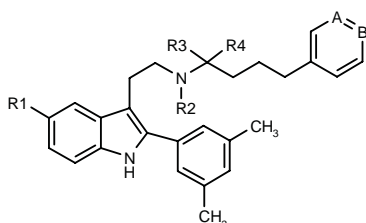
285574

1-[2-(3,5-Dimethylphenyl)-3-[2-[4-(4-pyridinyl)butylamino]-ethyl]-1*H*-indol-5-yl]-1-(4-morpholinyl)methanone



C32 H38 N4 O2; Mol wt: 510.6782

ACTION – Nonpeptide gonadotropin-releasing hormone (GnRH) antagonist expected to be useful in the treatment of a variety of sex hormone-related conditions in men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasias such as prostate, breast and ovarian cancer, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be useful as an adjunct in the treatment of growth hormone deficiency and short stature, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other exemplified compounds include the following:



Compound	R1	R2	R3=R4	A	B	Formula
285575	7-azabicyclo[2.2.1]-hept-7-yl-COC(Me)2	H	H	N	CH	C ₃₇ H ₄₆ N ₄ O
285576	1-Et-4,4-(Me)2-5-oxo-4,5-dihydro-1 <i>H</i> -pyrazol-3-yl	H	H	N	CH	C ₃₄ H ₄₁ N ₅ O
285577	4-Me-5-oxo-4,5-dihydro-1 <i>H</i> -tetrazol-1-yl	H	H	N	CH	C ₂₉ H ₃₃ N ₇ O
285578	7-azabicyclo[2.2.1]-hept-7-yl-COC(Me)2	H	Me	CH	N	C ₃₉ H ₅₀ N ₄ O
285579	7-azabicyclo[2.2.1]-hept-7-yl-COC(Me)2	Me	H	CH	N	C ₃₈ H ₄₈ N ₄ O

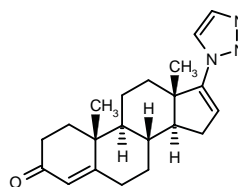
SOURCE – Merck & Co.

REFERENCES

1. Goulet, M. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. WO 0004013.

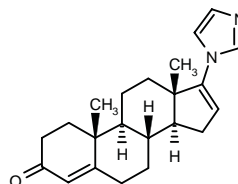
VN/85-1**261760**

17-(1*H*-1,2,3-Triazol-1-yl)androsta-4,16-dien-3-one



C21 H27 N3 O; Mol wt: 337.4643

ACTION – Antiandrogenic agent, a potent, noncompetitive inhibitor of human 17 α -hydroxylase/C_{17,20}-lyase (K_i = 1.2 nM, IC_{50} = 8 nM) with at least 30-fold greater activity than ketoconazole (K_i = 38 nM) and no inhibitory activity against human prostatic microsomal 5 α -reductase (IC_{50} ~ 400,000 nM). In adults rats, compound given s.c. at 50 mg/kg/day for 14 days significantly reduced serum and prostate testosterone and dihydrotestosterone levels, as well as prostate and seminal vesicle wet weight. Potentially useful for the treatment of androgen-dependent prostate cancer. Another related 17-azolyl steroid is:



VN/108-1 [261759]: C22 H28 N2 O

SOURCE – University of Maryland, Baltimore, MD (US).

REFERENCES

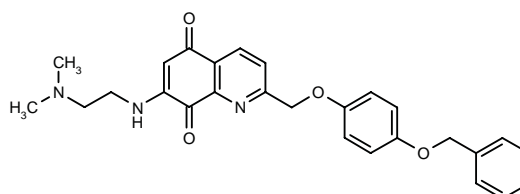
1. Njar, V.C.O. et al. *Novel 17-azolyl steroids, potent inhibitors of human cytochrome 17 α -hydroxylase-C17,20-lyase (P45017 α): Potential agents for the treatment of prostate cancer*. J Med Chem 1998, 41(6): 902.

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INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

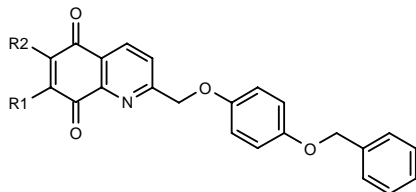
285112

2-[4-(Benzyloxy)phenoxyethyl]-7-[2-(dimethylamino)-ethylamino]-5,8-dihydroquinoline-5,8-dione



C27 H27 N3 O4; Mol wt: 457.5273

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase with the ability to inhibit the proliferation of human pulmonary cancer A549 cells (IC_{50} = 0.33 μ M). A representative compound from a series of quinoline-5,8-dione derivatives, wherein the following are also included:



Compound	R1	R2	Formula
285113	NHCH ₂ CH ₂ OH	H	C ₂₅ H ₂₂ N ₂ O ₅
285114	NHCH ₂ CH ₂ OCH ₂ CH ₂ OH	H	C ₂₇ H ₂₆ N ₂ O ₆
285115	NHCH ₂ CH ₂ N(Me) ₂	Cl	C ₂₇ H ₂₆ ClN ₃ O ₄
285116	H	SCH ₂ CH ₂ N(Me) ₂	C ₂₇ H ₂₆ N ₂ O ₄ S
285117	NHPh	Cl	C ₂₉ H ₂₁ ClN ₂ O ₄

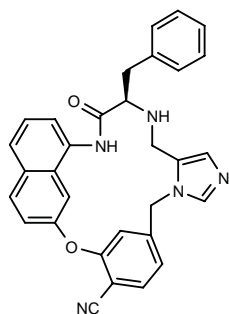
SOURCE – Kyowa Hakko.

REFERENCES

1. Tanba, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) *5,8-Quinolinedione derivs.* JP 1999335354.

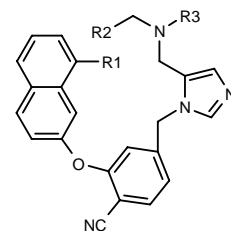
285237

20(*R*)-Benzyl-19-oxo-19,20,21,22-tetrahydro-5*H*,18*H*-12,14-etheno-6,10-methenobenzo[*d*]imidazo[4,3-*k*]-[1,6,9,12]oxatriazacyclooctadecine-9-carbonitrile

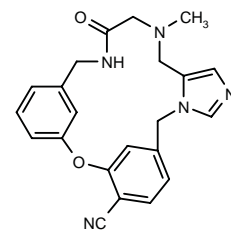


C₃₁ H₂₅ N₅ O₂; Mol wt: 499.5715

ACTION – An inhibitor of protein prenyltransferases and the prenylation of the oncogene protein Ras, with potential in the treatment or prevention of cancer, blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease, as well as for conferring radiation sensitivity to tumor cells. Other specifically claimed compounds from this series of non-thiol-containing peptidomimetic macrocyclic derivatives include the following:



Compound	R1,R2	R3	Formula
285240	-N(Me)CO-	Me	C ₂₆ H ₂₃ N ₅ O ₂
285241	-CONH-	H	C ₂₅ H ₂₁ N ₅ O ₂



285238: C₂₂ H₂₁ N₅ O₂

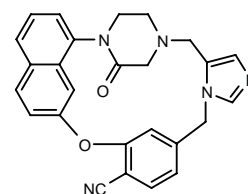
SOURCE – Merck & Co.

REFERENCES

1. Dinsmore, C.J. et al. (Merck & Co., Inc.) *Inhibitors of prenyl-protein transferase.* WO 0001701.

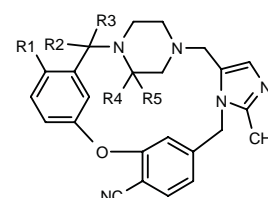
285242

(+)-19-Oxo-19,20-dihydro-5*H*,22*H*-18,21-ethano-12,14-etheno-6,10-methenobenzo[*d*]imidazo[4,3-*k*]-[1,6,9,12]oxatriazacyclooctadecine-9-carbonitrile

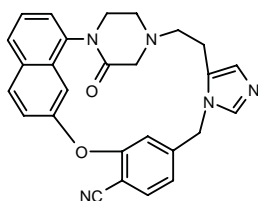


C₂₆ H₂₁ N₅ O₂; Mol wt: 435.4849

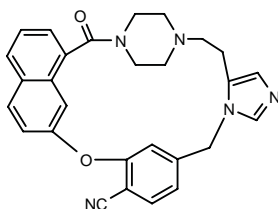
ACTION – An inhibitor of protein prenyltransferases and the prenylation of the oncogene protein Ras, with potential in the treatment or prevention of cancer, blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease, as well as for conferring radiation sensitivity to tumor cells. Other specifically claimed compounds from this series of peptidomimetic piperazine-containing macrocyclic derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
285243	Br	H	H	-O-		C ₂₄ H ₂₂ BrN ₅ O ₂
285244	cyclobutyl-CH ₂ CH ₂	-O-		H	H	C ₃₀ H ₃₃ N ₅ O ₂
285245	(CH ₂) ₄ CF ₃	H	H	-O-		C ₂₉ H ₃₀ F ₃ N ₅ O ₂



285247: C₂₇ H₂₃ N₅ O₂



285248: C₂₈ H₂₅ N₅ O₂

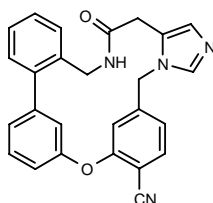
SOURCE – Merck & Co.

REFERENCES

1. Dinsmore, C.J. et al. (Merck & Co., Inc.) *Inhibitors of prenyl-protein transferase*. WO 0001702.

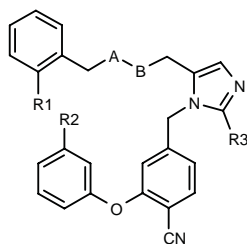
285249

23-Oxo-21,22,23,24-tetrahydro-5*H*-6,10:12,16-dime-thenobenzo[*g*]imidazo[4,3-*m*][1,8,12]oxadiazaeicosine-9-carbonitrile

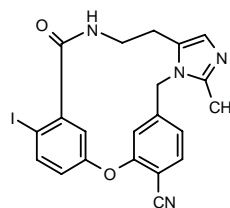


C₂₆ H₂₀ N₄ O₂; Mol wt: 420.4700

ACTION – An inhibitor of protein prenyltransferases and the prenylation of the oncogene protein Ras, with potential in the treatment or prevention of cancer, blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease, as well as for conferring radiation sensitivity to tumor cells. Other specifically claimed compounds from this series of non-thiol-containing peptidomimetic macrocyclic derivatives include the following:



Compound	R1,R2	R3	A	B	Formula
285250	bond	H	-CH ₂ -	-NH-	C ₂₆ H ₂₂ N ₄ O
285251	-NHCO-	H	-NH-	-CH ₂ -	C ₂₇ H ₂₃ N ₅ O ₂
285252	-N(Et)CO-	Me	-NH-	-CH ₂ -	C ₃₀ H ₂₉ N ₅ O ₂



285253: C₂₁ H₁₇ I N₄ O₂

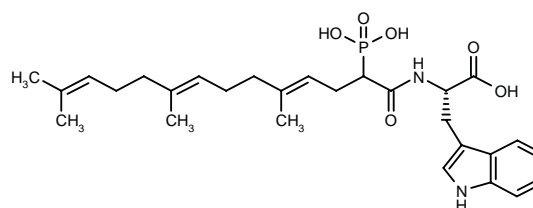
SOURCE – Merck & Co.

REFERENCES

1. Bell, I.M. et al. (Merck & Co., Inc.) *Inhibitors of prenyl-protein transferase*. WO 0001382.

285460

N-[5,9,13-Trimethyl-2-phosphonotetradeca-4(*E*),8(*E*),12-trienoyl]-L-tryptophan



C₂₈ H₃₉ N₂ O₆ P; Mol wt: 530.5981

ACTION – Agent for the treatment or prevention of cancer, atherosclerosis, restenosis and hepatitis delta infections, a potent and selective inhibitor of protein farnesyl-transferase (IC₅₀ = 10 nM vs. IC₅₀ = 4700 nM for protein geranylgeranyltransferase). A representative compound from a series of unsaturated phosphonates derived from indole.

SOURCE – Pierre Fabre.

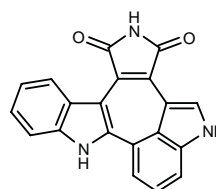
REFERENCES

1. Lamothe, M. and Halazy, S. (Pierre Fabre Médicament) *Unsaturated phosphonates derived from indole*. FR 2781228, WO 0004032.

ARCYRIACYANIN A

285030

5,9-Dihydro-1*H*-pyrrolo[3',4':6,7]cyclohepta[2,1-*b*:5,4,3-*c'*']-diindole-1,3(2*H*)-dione



C₂₀ H₁₁ N₃ O₂; Mol wt: 325.3259

ACTION – Antineoplastic agent, a slime mold pigment that can be derived biogenetically from arcylarubin A or synthesized and which acts as a protein kinase C (PKC) and protein tyrosine kinase inhibitor (1-100 µg/ml); it shows selectivity over protein kinase A (PKA) and calmodulin-dependent protein kinase C (inactive at up to 100 µg/ml). Compound showed broad-spectrum cytotoxic activity at micromolar concentrations against human cancer cell lines including breast, colon, lung, ovary and kidney cancer cells.

SOURCE – Showa College of Pharmaceutical Sciences, Tokyo (JP).

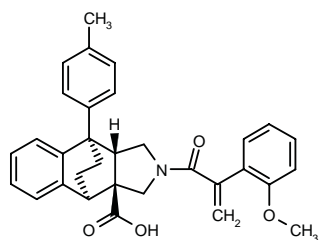
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1. Brenner, M. et al. *Pigments from fungi. 67. Total synthesis of the slime mold alkaloid arcylarubin A*. Chem Eur J 1997, 3(1): 70.
2. Murase, M. et al. *A new concise synthesis of arcylarubin A and its unique inhibitory activity against a panel of human cancer cell line*. Chem Pharm Bull 2000, 48(1): 81.
3. Murase, M. et al. *A synthesis of arcylarubin A, an unsymmetrically substituted indole pigment of the slime mold by palladium catalyzed cross-coupling reaction*. Chem Pharm Bull 1998, 46(6): 889.

RPR-130401*

268682

(3a*RS*,4*SR*,9*SR*,9a*RS*)-2-[2-(2-Methoxyphenyl)-2-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1*H*-4,9-ethanobenzo[*f*]isoindole-3a-carboxylic acid



C32 H31 N O4; Mol wt: 493.5999

ACTION – Antineoplastic agent, a protein farnesyltransferase inhibitor proven to inhibit cellular Ras processing and colony formation in a panel of Ki-Ras-mutated human cell lines including colon carcinoma HCT 116, colon adenoarcinoma SW620, lung carcinoma A549 and H460, and pancreas cancer MIA PaCa-2 cells at concentrations of 0.02-1 µM. *In vivo*, compound (400 mg/kg p.o. b.i.d. x 3 weeks) exhibited cytostatic activity against human colon carcinoma HCT116 xenografts in nude mice; combination with CPT-11 (irinotecan) at optimal doses produced greater antitumor activity compared to either agent alone and was well tolerated in these animals. Combination with the geranylgeranyltransferase-1 inhibitor GGTI-298 at nontoxic concentrations was found to efficiently block (80%) the proliferation of Ki-Ras-overexpressing transformed rat adrenocortical cells (RTAC) by blocking the cell cycle in the G0/G1 phase and disrupting MAP kinase activation.

SOURCE – Aventis Pharma.

REFERENCES

1. Bourzat, J.-D. et al. (Aventis Pharma SA) *Farnesyl transferase inhibitors*. EP 0948483, WO 9829390.
2. Mailliet, P. et al. *Benzo[*f*]perhydroisoindoles: A series of potent and selective inhibitors of the farnesylation of Ki-Ras*. Proc Amer Assoc Cancer Res 1998, 39: Abst 1845.
3. Mazet, J.L. et al. *Combination of the novel farnesyltransferase inhibitor RPR130401 and the geranylgeranyltransferase-1 inhibitor GGTI-298 disrupts MAP kinase activation and G(1)-S transition in Ki-Ras-overexpressing transformed adrenocortical cells*. FEBS Lett 1999, 460(2): 235.
4. Virgnaud, P. et al. *In vivo combination of RPR 130401, a non-peptidomimetic farnesyltransferase inhibitor, with chemotherapy*. Proc Amer Assoc Cancer Res 1999, 40: Abst 3453.
5. Virgnaud, P. et al. *RPR 130401, a non-peptidomimetic farnesyltransferase inhibitor with in vivo activity*. Proc Amer Assoc Cancer Res 1998, 39: Abst 1846.

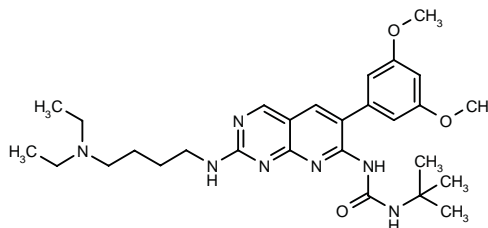
*Identified compound **268682** Drug Data Rep1998, 020(10): 0890.

ANGIOGENESIS INHIBITORS

PD-173074

261638

N-*tert*-Butyl-*N'*-[2-[4-(diethylamino)butylamino]-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidin-7-yl]urea



C28 H41 N7 O3; Mol wt: 523.6779

ACTION – Antiangiogenic agent that acts by inhibiting fibroblast growth factor (FGF) receptor 1 tyrosine kinase (FGFR1 TK; IC₅₀ = 26 nM) and shows high selectivity over other receptor tyrosine kinases including platelet-derived growth factor receptor β (PDGFR-β), c-Src, insulin receptor and epidermal growth factor receptor (EGFR) TKs and protein kinase C (PKC) (IC₅₀ = 15.5, 20.3, > 40, > 50 and > 40 µM, respectively). Compound strongly inhibited the growth of human umbilical vein endothelial cells (IC₅₀ = 60 nM) compared with a panel of tumor cell lines (IC₅₀ = 6.8-12 µM against sensitive and drug-resistant human breast cancer MDA-435 LCC6 and human fibrosarcoma HT-1080). In a murine angiogenesis model, compound was shown to inhibit the formation of microcapillaries on a subcutaneously implanted Matrigel plug. In addition, in mice bearing murine mammary 16c tumor, compound given orally at 30-60 mg/kg/day for 28 days dramatically prolonged the duration of the antitumor response to photodynamic therapy, without evidence of toxicity.

SOURCE – Warner-Lambert.

REFERENCES

1. Dimitroff, C.J. et al. *Anti-angiogenic activity of selected receptor tyrosine kinase inhibitors, PD 166285 and PD173074: Implications for combination treatment with photodynamic therapy.* Invest New Drugs 1999, 17(2): 121.

2. Dimitroff, C.J. et al. *Evaluation of the effects of PD166285, and PD173074 on in vitro and in vivo angiogenesis.* Proc Amer Assoc Cancer Res 1998, 39: Abst 653.

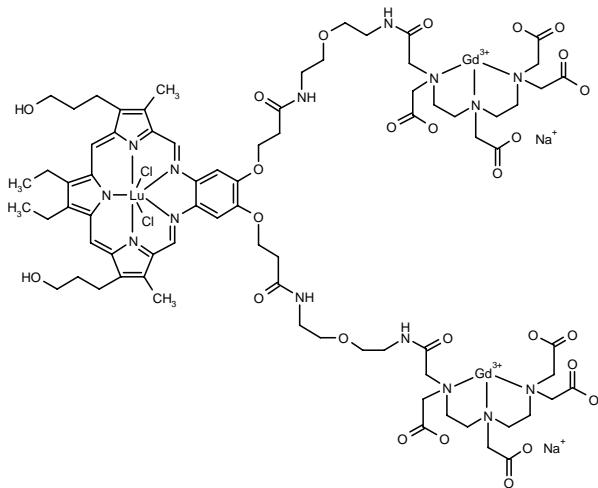
3. Mohammadi, M. et al. *Crystal structure of an angiogenesis inhibitor bound to the FGF receptor tyrosine kinase domain.* EMBO J 1998, 17(20): 5896.

4. Park, S. et al. *Inhibition of FGF-2-mediated cell proliferation in corneal endothelial cells by inhibitors specific for signal transduction.* Invest Ophthalmol Visual Sci 1999, 40(4): Abst 542.

OTHER ONCOLYTIC DRUGS

285074

Disodium (dichloro-1κ²-C)/[μ₃-[[21,21'-[[9,10-diethyl-5,14-bis(2-hydroxypropyl)-4,15-dimethyl-8,11-imino-3,6:16,13-dinitrilo-1,18-benzodiazacycloeicosine-20,21-diyl-1κ⁵N¹,N¹⁸,N²³,N²⁴,N²⁵]bis(oxy)]bis[3,6,9-tris(carboxy-2κO;3κO')methyl]-11-(oxo-2κO;3κO')-19-oxo-15-oxa-3,6,9,12,18-pentaazaheneicosanoato-2κ⁵N³,N⁶,N⁹,O¹;3κ⁵N^{3'},N^{6'},N^{9'},O^{1'}]](9-)]-2,3-digadolinium-1-lutetate(2-)



C76 H100 Cl2 Gd2 Lu N15 Na2 O26; Mol wt: 2246.0610

ACTION – Porphyrin complex useful for photodynamic therapy (PDT) and for magnetic resonance imaging (MRI) diagnosis, reported to possess good water solubility and good *in vivo* stability.

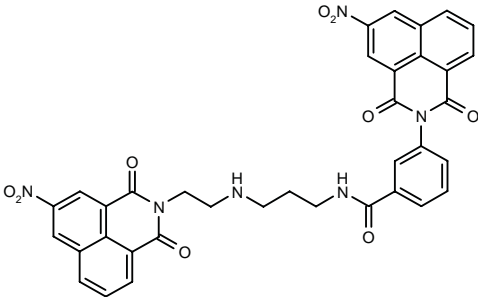
SOURCE – Schering AG.

REFERENCES

1. Platzek, J. et al. (Schering AG) *Porphyrin derivs. and their use in photodynamic therapy and MRI diagnosis.* DE 19831217, WO 0001698.

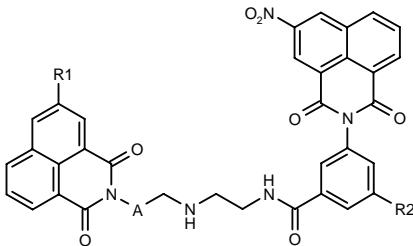
285293

3-(5-Nitro-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-2-yl)-*N*-[3-[2-(5-nitro-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-2-yl)ethylamino]propyl]benzamide

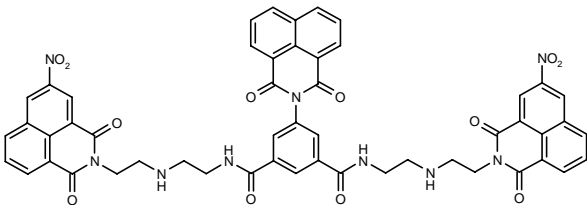


C36 H26 N6 O9; Mol wt: 686.6344

ACTION – Antineoplastic agent reported to possess high affinity for DNA and shown to exert potent cytotoxic activity against KB cells (IC₅₀ = 0.00023 μM). Other compounds within this series of naphthalimidobenzamide derivatives include the following:



Compound	R1	R2	A	Formula
285294	NO2	H	-(CH2)2-	C ₃₆ H ₂₆ N ₆ O ₉
285295	NO2	H	-CH2-	C ₃₅ H ₂₄ N ₆ O ₉
285296	H	1-Pip-CH2CH2NHCO	-CH2-	C ₄₃ H ₃₉ N ₇ O ₈



285297: C52 H39 N9 O12

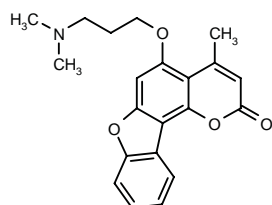
SOURCE – Taiho.

REFERENCES

1. Noguchi, K. et al. (Taiho Pharmaceutical Co., Ltd.) *Naphthalimidobenzamide derivs.* WO 0001672.

285310

5-[3-(Dimethylamino)propoxy]-4-methyl-2*H*-[1]benzofuro-[2,3-*h*][1]benzopyran-2-one



C21 H21 N O4; Mol wt: 351.3999

ACTION – Antineoplastic agent, a derivative of furocoumarin with strong photobiological activity. In the presence of UVA irradiation, compound exhibited strong cytotoxic activity against human cervix adenocarcinoma HeLa cells and human promyelocytic leukemia HL-60 cells (IC_{50} = 1.12 and 0.52 mM, respectively), being about 10-fold more potent than 8-methoxypsoralen (IC_{50} = 5.4 and 10 mM, respectively), but was devoid of cutaneous phototoxicity and was inactive in the absence of irradiation. Studies to identify intracellular targets other than DNA are currently in progress.

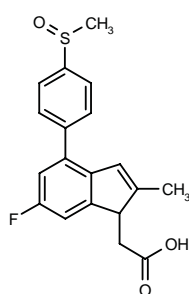
SOURCES – Universidad de Santiago de Compostela, Santiago de Compostela (ES); Università degli Studi di Padova, Padova (IT).

REFERENCES

1. Santana, L. et al. *A new benzoangelicin with strong photobiological activity*. Bioorg Med Chem Lett 2000, 10(2): 135.

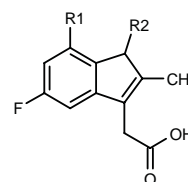
285525

2-[6-Fluoro-2-methyl-4-[4-(methylsulfinyl)phenyl]-1*H*-inden-1-yl]acetic acid

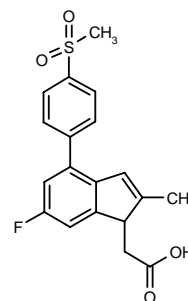


C19 H17 F O3 S; Mol wt: 344.4043

ACTION – Agent for inducing or promoting apoptosis and for arresting uncontrolled neoplastic cell proliferation, a representative compound from a series of substituted indenyl-3-acetic acid derivatives, wherein the following are also included:



Compound	R1	R2	Formula
285526	4-(MeSO)-PhCH2	H	C ₂₀ H ₁₉ FO ₃ S
285527	H	4-(MeSO)-PhNH	C ₁₉ H ₁₈ FNO ₃ S
285528	4-(MeSO)-PhCH2CH2	H	C ₂₁ H ₂₁ FO ₃ S
285530	4-(MeSO)-PhCO	H	C ₂₀ H ₁₇ FO ₄ S



285529: C₁₉ H₁₇ F O₄ S

SOURCE – Cell Pathways.

REFERENCES

1. Sperl, G. (Cell Pathways, Inc.) *Position 7-substd. indenyl-3-acetic acid derivs. and amides thereof for the treatment of hyperplasia*. US 6020379.

BEXAROTENE

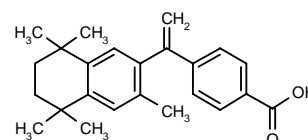
Prop INN

214151

4-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)vinyl]benzoic acid

LG-100069

LGD-1069⁺



C24 H28 O2; Mol wt: 348.4900

Fine white crystals, m.p. 234 °C.

ACTION – Retinoid X receptor (RXR)-selective retinoid with antiproliferative activity against certain tumor cell lines.

INDICATION – Treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.

PRESENTATION – Capsules, 75 mg.

PROPRIETARY NAME – *Targretin* (US).

SOURCE – Ligand.

RECENT REFERENCES

1. Agarwal, V.R. et al. *Targretin causes complete regression of mammary carcinoma by inducing adipocyte differentiation in mammary glands*. 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst OR28-4.
2. Agarwal, V.R. et al. *Targretin causes complete regression of mammary carcinoma by modulating differentiation in mammary glands*. Proc Amer Assoc Cancer Res 1999, 40: Abst 23.
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4. Bischoff, E.D. et al. *Tamoxifen resistance: The RXR-selective ligand LGD1069 causes complete regression of tamoxifen resistant mammary carcinoma*. Proc Amer Assoc Cancer Res 1999, 40: Abst 2054.
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*Drug Data Rep 1995, 017(01): 0094.

CELECOXIB⁺

Prop INN;USAN

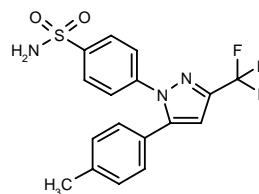
New indication

228583

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]-benzenesulfonamide

SC-58635

YM-177



C17 H14 F3 N3 O2 S; Mol wt: 381.3766

ACTION – Nonsteroidal antiinflammatory drug that selectively inhibits cyclooxygenase type 2 (COX-2), originally marketed for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis in adults*.

INDICATION – For reducing the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP) as an adjunct to usual care.

PRESENTATION – Capsules, 100 and 200 mg.

PROPRIETARY NAME – Celebrex (US).

SOURCES – Pfizer; Pharmacia.

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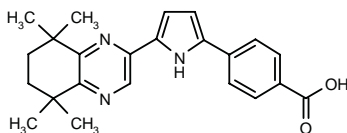
*First introduced in January 1999 in the U.S.

*Drug Data Rep 1997, 019(02): 0161.

ER-34617*

247716

4-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydroquinoxalin-2-yl)-1H-pyrrol-2-yl]benzoic acid



C23 H25 N3 O2; Mol wt: 375.4750

ACTION – Retinoic acid receptor (RAR) agonist with high selectivity for RAR α over RAR β and RAR γ receptors, as well as over retinoid X receptors (RXRs). When compared with *all-trans*-retinoic acid (ATRA), compound exhibited more potent agonist activity at RAR α receptors, and was at least 8-fold more active in cell differentiation-inducing activity in HL-60 cells (ED₃₀ = 0.11 and 0.94 nM for compound and ATRA, respectively).

SOURCE – Eisai.

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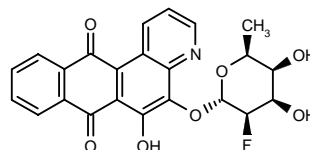
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*Identified compound **247716** Drug Data Rep 1997, 019(06): 0562.

FT-Alz

285743

5-(2,6-Dideoxy-2-fluoro- α -L-talopyranosyloxy)-6-hydroxy-naphtho[2,3-f]quinoline-7,12-dione



C23 H18 F N O7; Mol wt: 439.3932

ACTION – Antineoplastic agent with a broad spectrum of cytotoxic activity *in vitro* against a panel of human tumor cell lines including gastric adenocarcinoma MKN-1 (IC₅₀ = 0.73 μ M), lung carcinoma PC-14 (IC₅₀ = 0.71 μ M), bladder carcinoma T-24 (IC₅₀ = 0.36 μ M), nasopharyngeal carcinoma KB (IC₅₀ = 0.27 μ M), melanoma HMV-1 (IC₅₀ = 0.59 μ M) and leukemia K562 (IC₅₀ = 0.71 μ M), as well as murine leukemia P388 and L1210 cells (IC₅₀ = 0.77 and 0.32 μ M, respectively); compound was also active against doxorubicin-resistant P388 cells (IC₅₀ = 0.82 μ M) and was able to reverse multidrug resistance mediated by P-glycoprotein in human ovarian carcinoma 2780AD cells. In addition, compound showed strong topoisomerase II-inhibitory activity (IC₅₀ = 5 μ M) and was able to induce apoptosis in human monocytic leukemia cells.

SOURCES – Institute of Bioorganic Chemistry, Kawasaki (JP); Keio University, Yokohama (JP).

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GFMO-1

Growth factor modulator polypeptide 1

285021

ACTION – Human growth factor modulator, a polypeptide for use in the diagnosis, treatment or prevention of disorders associated with the expression of growth factors, especially cancer and fibrotic disorders. Polynucleotides encoding this polypeptide, as well as expression vectors, host cells, antibodies, agonists and antagonists, are also disclosed. Another related polypeptide is:

Growth factor modulator polypeptide 2

GFMO-2 [285023]

SOURCE – Incyte.

REFERENCES

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ISIS-17509

284344

20-Mer antisense chimeric oligonucleotide whose sequence is: 5'-TGGAGTGTCTTTCTGGTCA-3', in which the ten central nucleotides are 2'-deoxynucleotides and their internucleotide linkage is phosphorothioate, and the last five nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides and their internucleotide linkage is phosphodiester; all the cytidines throughout the oligonucleotide are 5-methylcytidines

ACTION – Antisense chimeric phosphorothioate oligonucleotide targeted to nucleic acids encoding the human antiapoptotic bcl-2-related protein A1, potentially useful for modulating the expression of this protein and for the treatment of diseases for which promotion of apoptosis is desirable, such as in tumors. Compound produced 93.3% inhibition of A1 expression in human umbilical vein endothelial cells (HUVEC) at 100 nM. Also included are antisense oligonucleotides targeted to human mcl-1, a representative of which is:

20-Mer antisense chimeric phosphorothioate oligonucleotide whose sequence is: 5'-CAAATGTCTC-TCCATCCACC-3', in which the ten central nucleotides are 2'-deoxynucleotides, the last five nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides and all the cytidines throughout the oligonucleotide are 5-methylcytidines

ISIS-20416 [284345]

SOURCE – Isis Pharmaceuticals.

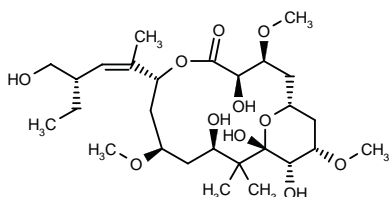
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PELORUSIDE A

284984

(1*S*,3*S*,4*R*,7*R*,9*R*,11*R*,13*S*,14*S*,15*S*)-4,11,13,14-Tetrahydroxy-7-[3(*S*)-(hydroxymethyl)-1-methyl-1(*Z*)-penteny]-3,9,15-trimethoxy-12,12-dimethyl-6,17-dioxabicyclo[11.3.1]heptadecan-5-one



C27 H48 O11; Mol wt: 548.6652

$[\alpha]_D^{20} +16^\circ$ (c 0.30, CH₂Cl₂).

ACTION – Antineoplastic macrolide isolated from the New Zealand marine sponge *Mycale* sp., found to be cytotoxic to murine leukemia P388 cells at approximately 10 ng/ml (18 nM).

SOURCE – Victoria University of Wellington, Wellington (NZ).

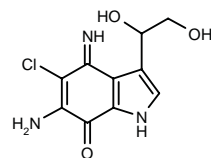
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SECOBATZELLINE A

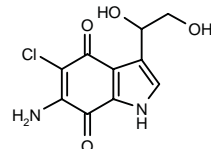
285319

6-Amino-5-chloro-3-(1,2-dihydroxyethyl)-4-imino-4,7-dihydro-1*H*-indol-7-one



C10 H10 Cl N3 O3; Mol wt: 255.6600

ACTION – Antiinflammatory, immunomodulating, neuroprotective and antineoplastic agent isolated from a marine sponge of the genus *Batzella*. Compound was found to inhibit caspase 3 (CPP32; IC₅₀ = 0.02 µg/ml), as well as the growth of murine leukemia P388 (IC₅₀ = 0.06 µg/ml) and human lung adenocarcinoma A549 cells (IC₅₀ = 0.04 µg/ml). In addition, it was tested in a mixed lymphocyte reaction (MLR) and lymphocyte viability (LCV) assays, exhibiting IC₅₀ values of 0.68 and 1.4 µg/ml, respectively. Another compound isolated from the same source is:



Secobatzelline B [285320]: C10 H9 Cl N2 O4

SOURCE – Harbor Branch Oceanographic Institution, Fort Pierce, FL (US).

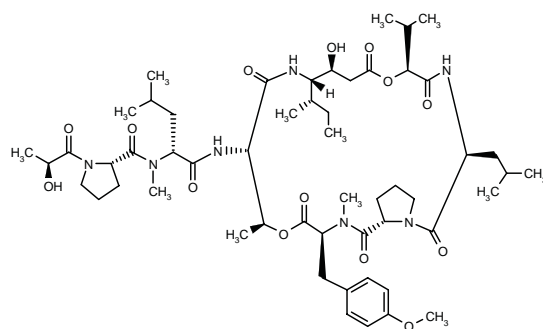
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TAMANDARIN A¹⁻³

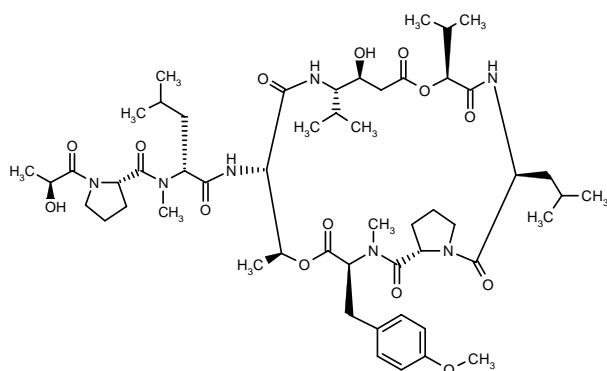
285367

(3*S*,6*S*,10*S*,11*S*,14*R*,15*S*,18*S*,21*S*)-14-[*N*-[2(*S*)-Hydroxypropionyl]-*L*-prolyl-*D*-(*N*-methyl)leucylamino]-10-hydroxy-3-isobutyl-6-isopropyl-18-(4-methoxybenzyl)-15,19-dimethyl-11-[1(*S*)-methylpropyl]-7,16-dioxabicyclo[19.3.0]tetracosane-2,5,8,13,17,20-hexaone



C54 H85 N7 O14; Mol wt: 1056.3010

ACTION – Cytotoxic depsipeptide extracted from an unidentified Brazilian marine ascidian of the family Didemnidae, with cytotoxic activity in various human tumor cell lines including pancreatic carcinoma BX-PC3 ($IC_{50} = 1.79$ ng/ml), prostatic cancer DU-145 ($IC_{50} = 1.36$ ng/ml) and head and neck carcinoma UMSCC10b ($IC_{50} = 0.99$ ng/ml); didemnin B, an immunosuppressive and antitumor peptide structurally related to compound, exhibited slightly less cytotoxic activity. Although the mechanism of action of the compound has not been clarified, it inhibited protein biosynthesis in rabbit reticulocyte cell lysates with an IC_{50} of $1.3 \mu M$, and was approximately 3-fold more potent than didemnin B in this assay. Another related compound from this source is:



Tamandarin B³ [285368]²: C53 H83 N7 O14

SOURCES – Universidade Federal Fluminense, Rio de Janeiro (BR); University of California, San Diego, La Jolla, CA (US).

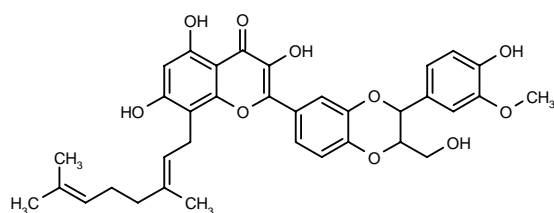
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

285313

8-[3,7-Dimethyl-2(*E*),6-octadienyl]-3,5,7-trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-4*H*-1-benzopyran-4-one



C35 H36 O10; Mol wt: 616.6594

ACTION – Potential multidrug resistance (MDR)-reversing agent, a P-glycoprotein modulator with high affinity for the recombinant nucleotide-binding domain (NBD2) of P-glycoprotein ($K_d = 0.12 \mu M$).

SOURCE – Université Claude Bernard Lyon 1, Villeurbanne Cedex (FR).

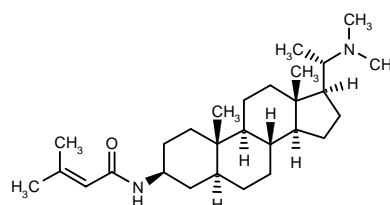
REFERENCES

1. Maitrejean, M. et al. *The flavanolignan silybin and its hemisynthetic derivatives, a novel series of potential modulators of P-glycoprotein*. *Bioorg Med Chem Lett* 2000, 10(2): 157.

EPIPACHYSAMINE E¹⁻³

285669

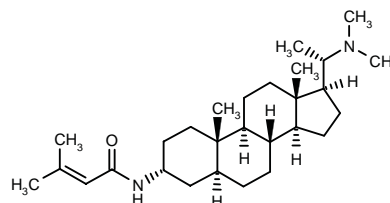
N-[20(*S*)-(Dimethylamino)-5 α -pregnan-3 β -yl]-3-methyl-2-butenamide



C28 H48 N2 O; Mol wt: 428.7002

Colorless powder.

ACTION – Multidrug resistance (MDR)-reversing agent, an alkaloid extracted from the Japanese plant *Pachysandra terminalis* that is able to modulate the sensitivity of doxorubicin-resistant murine leukemia P388 cells (P388/ADM) to antitumor drugs such as doxorubicin, etoposide and mitoxantrone. When compound was administered alone to P388 and P388/ADM cells it showed comparable cytotoxic activity ($IC_{50} = 0.56$ and $0.66 \mu g/ml$, respectively), and when it was added to P388/ADM cells at concentrations associated with low cytotoxicity (0.125-0.5 $\mu g/ml$), the cytotoxicity of doxorubicin, etoposide and mitoxantrone increased up to 4.6-fold. Another alkaloid extracted from *P. terminalis* is:



Pachysamine E [285614]¹: C28 H48 N2 O

SOURCES – Aomori University, Aomori (JP); Tohoku University, Sendai (JP).

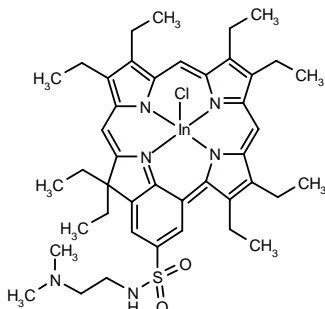
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PHOTOSENSITIZERS

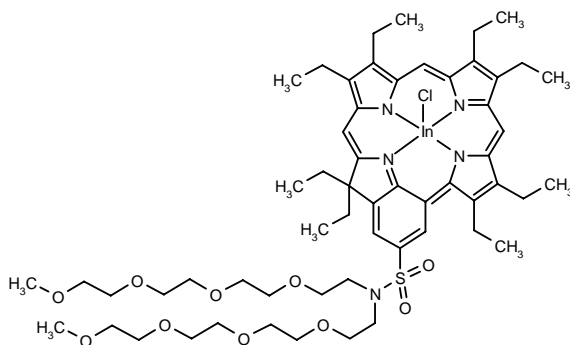
285128

Chloro[[N-[2-(dimethylamino)ethyl]-3,3,7,8,12,13,17,18-octaethyl-3*H*-benzo[*a*]porphyrin-2²-ylsulfonamido](2-)]-indium



C43 H56 Cl In N6 O2 S; Mol wt: 871.2944

ACTION – Photosensitizing agent for use in the photodynamic therapy (PDT) of disorders including cancer, atherosclerosis, benign prostatic hyperplasia, glaucoma and restenosis. When tested in mice bearing BA mammary tumors, compound produced 100% cure at 30 days after treatment with 0.05 $\mu\text{mol/kg}$ i.v. followed after 24 h by light irradiation from a laser source at 200 J/cm². Another compound from this series of indium pyrrolic macrocycles is:



285129: C57 H83 Cl In N5 O10 S

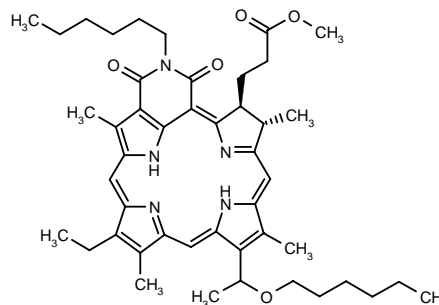
SOURCE – Miravant.

REFERENCES

1. Robinson, B.C. and Phadke, A.S. (Miravant Medical Technologies) *Indium photosensitizers for PDT*. WO 0000204.

285308

3-[7-Ethyl-2²-hexyl-12-[1-(hexyloxy)ethyl]-3,8,13,17(*S*)-tetramethyl-21,23-dioxo-2¹,2²,2³,18-tetrahydro-17*H*-pyrido[3,4,5-*a*]porphyrin-18(*S*)-yl]propionic acid methyl ester



C46 H61 N5 O5; Mol wt: 764.0179

ACTION – Photosensitizing agent for the photodynamic therapy (PDT) of cancer with excellent tumor uptake (7.27 $\mu\text{mol/kg}$) and tumor versus muscle ratio (8:1), as well as good photodynamic efficacy in mice inoculated with RIF (radiation-inducing fibrosarcoma) and treated with laser light; compound was able to induce 100% tumor cure when administered at 1 $\mu\text{mol/kg/day}$ for 30 days.

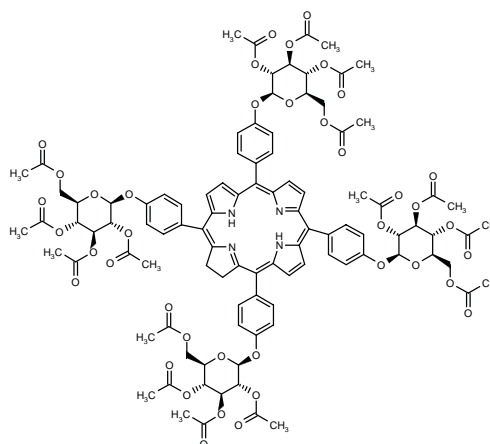
SOURCE – Roswell Park Cancer Institute, Buffalo, NY (US).

REFERENCES

1. Zheng, G. et al. *Photosensitizers related to purpurin-18-N-alkylimides: A comparative in vivo tumoricidal ability of ester versus amide functionalities*. Bioorg Med Chem Lett 2000, 10(2): 123.

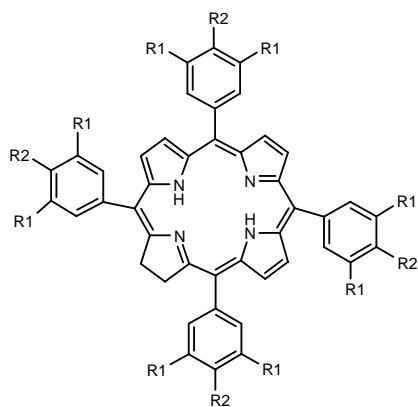
285422

5,10,15,20-Tetrakis[4-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)phenyl]-2,3-dihydroporphyrin



C100 H104 N4 O40; Mol wt: 2001.9100

ACTION – Photosensitizing agent for use in photodynamic therapy, also reported to possess cytotoxic effects. Other exemplified compounds from this series of porphyrin derivatives include the following:



Compound	R1	R2	Formula
285423	H	β-D-glucopyranosyloxy	C ₆₈ H ₇₂ N ₄ O ₂₄
285424	H	2,3,4,6-tetra-O-(Ac)-β-D-galactopyranosyloxy	C ₁₀₀ H ₁₀₄ N ₄ O ₄₀
285425	H	β-D-galactopyranosyloxy	C ₆₈ H ₇₂ N ₄ O ₂₄
285427	2,3,4,6-tetra-O-(Ac)-β-D-glucopyranosyloxy	H	C ₁₅₆ H ₁₇₆ N ₄ O ₈₀

SOURCE – Wyeth Lederle Japan.

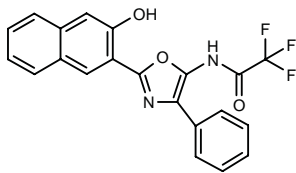
REFERENCES

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OCULAR MEDICATIONS

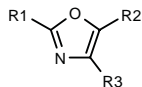
285331

2,2,2-Trifluoro-*N*-[2-(3-hydroxynaphthalen-2-yl)-4-phenyl-oxazol-5-yl]acetamide



C21 H13 F3 N2 O3 ; Mol wt: 398.3387

ACTION – Antiangiogenic agent, an inhibitor of tyrosine kinases with selectivity for vascular endothelial growth factor (VEGF) receptor tyrosine kinase. Potentially useful in the treatment of ocular neovascularization disorders such as diabetic retinopathy, as well as in the treatment of cancer, atherosclerosis and inflammatory disorders. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
285332	3-OH-2-Naph	NHAc	Ph	C ₂₁ H ₁₆ N ₂ O ₃
285333	3-OH-2-Naph	NHCOCF ₃	3-thienyl	C ₁₉ H ₁₁ F ₃ N ₂ O ₃ S
285334	3-OH-2-Naph	NHAc	3-thienyl	C ₁₉ H ₁₄ N ₂ O ₃ S
285335	2-NH2-3-quinolyl	2-oxo-1-pyrrolidinyl	Ph	C ₂₂ H ₁₈ N ₄ O ₂
285336	5-(3-thienyl)-3-Pyr	2-oxo-1-pyrrolidinyl	Ph	C ₂₂ H ₁₇ N ₃ O ₂ S
285337	2-OH-5-MeO-Ph	2-oxo-1-pyrrolidinyl	Ph	C ₂₀ H ₁₈ N ₂ O ₄

SOURCE – Merck & Co.

REFERENCES

1. Fraley, M.E. et al. (Merck & Co., Inc.) *Novel angiogenesis inhibitors.* WO 0002871.

VERTEPORFIN⁺

Rec INN; USAN

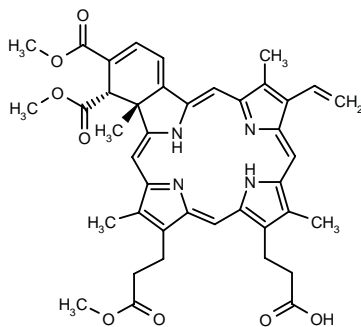
215967

A 1:1 mixture of benzoporphyrin derivative regioisomers CL-315555 and CL-315585

BPD-MA
CL-318952

221094

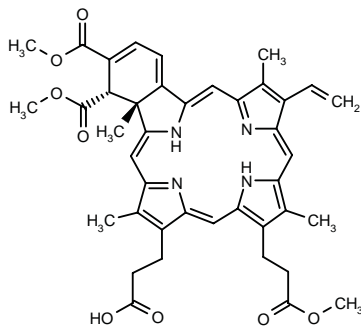
trans-2³,2⁴-Bis(methoxycarbonyl)-3,7,13,18-tetramethyl-17-vinyl-2⁴,3-dihydro-21*H*,23*H*-benzo[*b*]porphyrin-8,12-dipropionic acid 8-monomethyl ester



C41 H42 N4 O8 ; Mol wt: 718.80

221095

trans-2³,2⁴-Bis(methoxycarbonyl)-3,7,13,18-tetramethyl-17-vinyl-2⁴,3-dihydro-21*H*,23*H*-benzo[*b*]porphyrin-8,12-dipropionic acid 12-monomethyl ester



C41 H42 N4 O8 ; Mol wt: 718.80

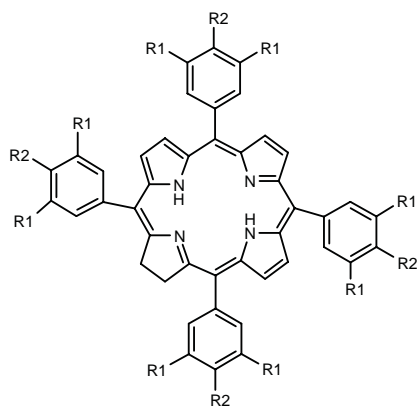
ACTION – Photosensitizer, a benzoporphyrin derivative that is activated by light to form cytotoxic products.

INDICATION – Photodynamic therapy of wet age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.

PRESENTATION – Vials (15 mg), powder for reconstitution as solution for i.v. injection, 2 mg/ml.

PROPRIETARY NAME – Visudyne (CH).

SOURCES – Ciba Vision; QLT PhotoTherapeutics.



Compound	R1	R2	Formula
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285424	H	2,3,4,6-tetra-O-(Ac)-β-D-galactopyranosyloxy	C ₁₀₀ H ₁₀₄ N ₄ O ₄₀
285425	H	β-D-galactopyranosyloxy	C ₆₈ H ₇₂ N ₄ O ₂₄
285427	2,3,4,6-tetra-O-(Ac)-β-D-glucopyranosyloxy	H	C ₁₅₆ H ₁₇₆ N ₄ O ₈₀

SOURCE – Wyeth Lederle Japan.

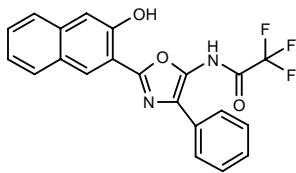
REFERENCES

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OCULAR MEDICATIONS

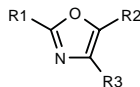
285331

2,2,2-Trifluoro-*N*-[2-(3-hydroxynaphthalen-2-yl)-4-phenyl-oxazol-5-yl]acetamide



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285334	3-OH-2-Naph	NHAc	3-thienyl	C ₁₉ H ₁₄ N ₂ O ₃ S
285335	2-NH2-3-quinolyl	2-oxo-1-pyrrolidinyl	Ph	C ₂₂ H ₁₈ N ₄ O ₂
285336	5-(3-thienyl)-3-Pyr	2-oxo-1-pyrrolidinyl	Ph	C ₂₂ H ₁₇ N ₃ O ₂ S
285337	2-OH-5-MeO-Ph	2-oxo-1-pyrrolidinyl	Ph	C ₂₀ H ₁₈ N ₂ O ₄

SOURCE – Merck & Co.

REFERENCES

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VERTEPORFIN+

Rec INN; USAN

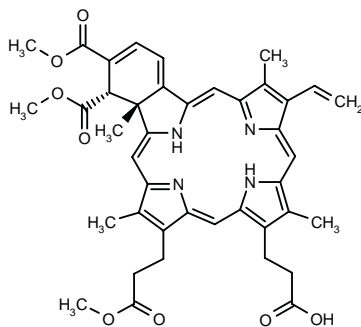
215967

A 1:1 mixture of benzoporphyrin derivative regioisomers CL-315555 and CL-315585

BPD-MA
CL-318952

221094

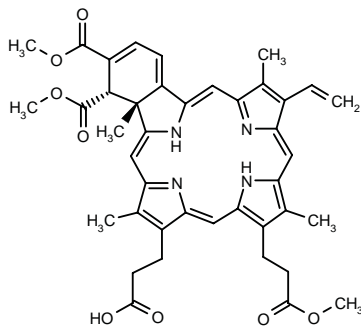
trans-2³,2⁴-Bis(methoxycarbonyl)-3,7,13,18-tetramethyl-17-vinyl-2⁴,3-dihydro-21*H*,23*H*-benzo[*b*]porphyrin-8,12-dipropionic acid 8-monomethyl ester



C41 H42 N4 O8 ; Mol wt: 718.80

221095

trans-2³,2⁴-Bis(methoxycarbonyl)-3,7,13,18-tetramethyl-17-vinyl-2⁴,3-dihydro-21*H*,23*H*-benzo[*b*]porphyrin-8,12-dipropionic acid 12-monomethyl ester



C41 H42 N4 O8 ; Mol wt: 718.80

ACTION – Photosensitizer, a benzoporphyrin derivative that is activated by light to form cytotoxic products.

INDICATION – Photodynamic therapy of wet age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.

PRESENTATION – Vials (15 mg), powder for reconstitution as solution for i.v. injection, 2 mg/ml.

PROPRIETARY NAME – Visudyne (CH).

SOURCES – Ciba Vision; QLT PhotoTherapeutics.

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2. Barbazetto, I.A. and Schmidt-Erfurth, U.M. *Photodynamic therapy (PDT) in the treatment of intraocular angioma*. 103rd Annu Meet Am Acad Ophthalmol (Oct 24-27, Orlando) 1999, Abst 090.

3. Bressler, N.M. *Photodynamic therapy with verteporfin of subfoveal choroidal neovascularization in age-related macular degeneration (AMD): Baseline characteristics and safety in the TAP randomized clinical trials*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 2113.

4. Coscas, G. *Photodynamic therapy with verteporfin in the treatment of neovascular AMD*. 12th Congr Eur Soc Ophthalmol (June 27-July 1, Stockholm) 1999, Abst SY3.

5. Chowdhary, R.K. et al. *Uptake of Verteporfin(R) by articular tissue following systemic and intra-articular administration*. Biopharm Drug Dispos 1998, 19(6): 395.

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9. Reinke, M.H. et al. *Verteporfin photodynamic therapy retreatment of normal retina and choroid in the cynomolgus monkey*. Ophthalmology 1999, 106(10): 1915.

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16. *Ciba Vision and QLT initiate T-IND clinical program for Visudyne therapy*. DailyDrugNews.com (Daily Essentials) 1999, Sept 14.

17. *Ciba Vision and QLT PhotoTherapeutics seek approval for Visudyne in U.S., Switzerland*. DailyDrugNews.com (Daily Essentials) 1999, Aug 19.

18. *FDA advisory committee to review Visudyne NDA*. DailyDrugNews.com (Daily Essentials) 1999, Oct 8.

19. *FDA advisory panel recommends approval of Visudyne therapy for wet AMD*. DailyDrugNews.com (Daily Essentials) 1999, Nov 18.

20. *FDA grants priority review to Visudyne NDA*. DailyDrugNews.com (Daily Essentials) 1999, Aug 25.

21. *FDA issues approvable letter for Visudyne*. DailyDrugNews.com (Daily Essentials) 2000, Feb 14.

22. *New hope for AMD sufferers: verteporfin proves effective and safe in TAP investigation*. DailyDrugNews.com (Daily Essentials) 1999, Jan 8.

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31. *Visudyne market introduction announced*. DailyDrugNews.com (Daily Essentials) 2000, Feb 2.

32. *Visudyne submitted for marketing approval in Canada*. DailyDrugNews.com (Daily Essentials) 1999, Nov 8.

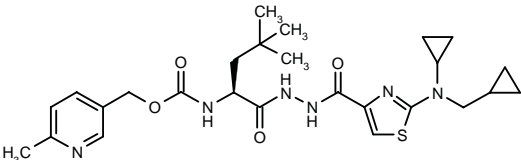
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

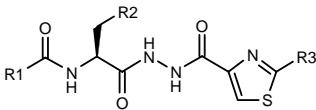
284811

N'-[2-[N-Cyclopropyl-N-(cyclopropylmethyl)amino]thiazol-4-ylcarbonyl]-N-α-(6-methylpyridin-3-ylmethoxycarbonyl)-L-(4-methyl)-leucylhydrazide



C26 H36 N6 O4 S; Mol wt: 528.6744

ACTION – An inhibitor of cysteine proteases, particularly cathepsin K, with potential in the treatment of diseases involving excessive bone loss or cartilage or matrix degradation such as osteoporosis, gingivitis, periodontitis, osteoarthritis, rheumatoid arthritis, Paget’s disease, hypercalcemia of malignancy and metabolic bone disease. Other specifically claimed compounds from this series of diacyl hydrazine derivatives include the following:



Compound	R1	R2	R3	Formula
284814	3,4-(F)2-Ph	i-Pr	i-BuN-(cyclopropyl)	C ₂₄ H ₃₁ F ₂ N ₅ O ₃ S
284819	4-(2-Pyr)-Ph	i-Pr	cyclopropyl-CH2-N(cyclopropyl)	C ₂₉ H ₃₄ N ₆ O ₃ S
284831	2-Me-5-imidazolyl	cyclopropyl	i-BuN-(cyclopentyl)	C ₂₄ H ₃₈ N ₇ O ₃ S
284832	4-(CH2OH)-Ph	cyclopropyl	i-BuN-(cyclopentyl)	C ₂₇ H ₃₇ N ₅ O ₄ S
284833	5-Me-2-Ph-4-oxazolyl	i-Pr	i-BuN-(cyclopropyl)	C ₂₈ H ₃₆ N ₆ O ₄ S
284835	5,6-(MeO)2-2-indolyl	cyclopropyl	i-BuN-(cyclopropyl)	C ₃₀ H ₄₀ N ₆ O ₅ S
284837	2-indolyl	cyclopropyl	i-BuN-(cyclopropyl)	C ₂₆ H ₃₂ N ₆ O ₃ S
284838	7-MeO-1,3-benzodioxol-5-yl	i-Pr	i-BuN-(cyclopropyl)	C ₂₆ H ₃₈ N ₅ O ₆ S

RECENT REFERENCES

1. Arnold, J. *Verteporfin therapy for the treatment of subfoveal choroidal neovascularization in age-related macular degeneration (AMD): Baseline characteristics and safety in the TAP randomized clinical trials*. 12th Congr Eur Soc Ophthalmol (June 27-July 1, Stockholm) 1999, Abst FP10.

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8. Mones, J. *Photodynamic therapy (PDT) with verteporfin of subfoveal choroidal neovascularization in age-related macular degeneration: Study design and baseline characteristics in the VIP randomized clinical trial*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 1703.

9. Reinke, M.H. et al. *Verteporfin photodynamic therapy retreatment of normal retina and choroid in the cynomolgus monkey*. Ophthalmology 1999, 106(10): 1915.

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16. Ciba Vision and QLT initiate T-IND clinical program for Visudyne therapy. DailyDrugNews.com (Daily Essentials) 1999, Sept 14.

17. Ciba Vision and QLT PhotoTherapeutics seek approval for Visudyne in U.S., Switzerland. DailyDrugNews.com (Daily Essentials) 1999, Aug 19.

18. FDA advisory committee to review Visudyne NDA. DailyDrugNews.com (Daily Essentials) 1999, Oct 8.

19. FDA advisory panel recommends approval of Visudyne therapy for wet AMD. DailyDrugNews.com (Daily Essentials) 1999, Nov 18.

20. FDA grants priority review to Visudyne NDA. DailyDrugNews.com (Daily Essentials) 1999, Aug 25.

21. FDA issues approvable letter for Visudyne. DailyDrugNews.com (Daily Essentials) 2000, Feb 14.

22. New hope for AMD sufferers: verteporfin proves effective and safe in TAP investigation. DailyDrugNews.com (Daily Essentials) 1999, Jan 8.

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25. QLT and Ciba Vision initiate phase IIIb verteporfin trial. DailyDrugNews.com (Daily Essentials) 1998, March 20.

26. QLT begins phase II trial for psoriasis treatment. DailyDrugNews.com (Daily Essentials) 1999, Aug 24.

27. QLT PhotoTherapeutics updates shareholders. DailyDrugNews.com (Daily Essentials) 1998, May 13.

28. Swiss regulatory authorities grant Visudyne therapy its first approval. DailyDrugNews.com (Daily Essentials) 1999, Dec 20.

29. Verteporfin proven safe in phase III trials. DailyDrugNews.com (Daily Essentials) 1998, May 15.

30. Visudyne filed for marketing approval with EMEA. DailyDrugNews.com (Daily Essentials) 1999, Aug 11.

31. Visudyne market introduction announced. DailyDrugNews.com (Daily Essentials) 2000, Feb 2.

32. Visudyne submitted for marketing approval in Canada. DailyDrugNews.com (Daily Essentials) 1999, Nov 8.

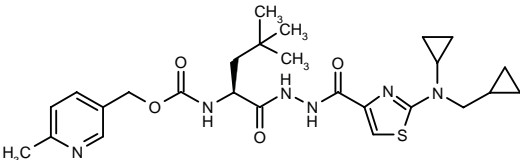
*Drug Data Rep 1995, 017(05): 0457.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

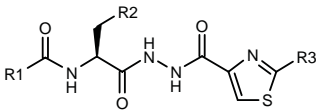
284811

N'-[2-[N-Cyclopropyl-N-(cyclopropylmethyl)amino]thiazol-4-ylcarbonyl]-N-α-(6-methylpyridin-3-ylmethoxycarbonyl)-L-(4-methyl)-leucylhydrazide

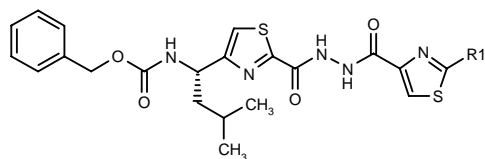


C26 H36 N6 O4 S; Mol wt: 528.6744

ACTION – An inhibitor of cysteine proteases, particularly cathepsin K, with potential in the treatment of diseases involving excessive bone loss or cartilage or matrix degradation such as osteoporosis, gingivitis, periodontitis, osteoarthritis, rheumatoid arthritis, Paget’s disease, hypercalcemia of malignancy and metabolic bone disease. Other specifically claimed compounds from this series of diacyl hydrazine derivatives include the following:



Compound	R1	R2	R3	Formula
284814	3,4-(F)2-Ph	i-Pr	i-BuN-(cyclopropyl)	C ₂₄ H ₃₁ F ₂ N ₅ O ₃ S
284819	4-(2-Pyr)-Ph	i-Pr	cyclopropyl-CH2-N(cyclopropyl)	C ₂₉ H ₃₄ N ₆ O ₃ S
284831	2-Me-5-imidazolyl	cyclopropyl	i-BuN-(cyclopentyl)	C ₂₄ H ₃₈ N ₇ O ₃ S
284832	4-(CH2OH)-Ph	cyclopropyl	i-BuN-(cyclopentyl)	C ₂₇ H ₃₇ N ₅ O ₄ S
284833	5-Me-2-Ph-4-oxazolyl	i-Pr	i-BuN-(cyclopropyl)	C ₂₈ H ₃₈ N ₆ O ₄ S
284835	5,6-(MeO)2-2-indolyl	cyclopropyl	i-BuN-(cyclopropyl)	C ₃₀ H ₄₀ N ₆ O ₅ S
284837	2-indolyl	cyclopropyl	i-BuN-(cyclopropyl)	C ₂₆ H ₃₂ N ₆ O ₃ S
284838	7-MeO-1,3-benzodioxol-5-yl	i-Pr	i-BuN-(cyclopropyl)	C ₂₆ H ₃₈ N ₅ O ₆ S



Compound	R1	Formula
284816	1-Naph	C ₃₁ H ₂₉ N ₅ O ₄ S ₂
284818	cyclopropyl-CH ₂ N(cyclopropyl)	C ₂₈ H ₃₄ N ₆ O ₄ S ₂

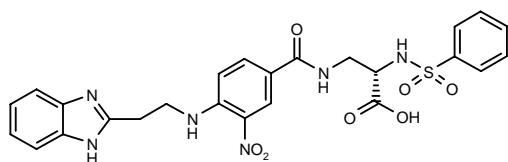
SOURCE – SmithKline Beecham.

REFERENCES

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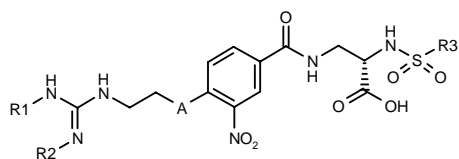
285122

3-[4-[2-(1*H*-Benzimidazol-2-yl)ethylamino]-3-nitro-benzamido]-2(*S*)-(phenylsulfonamido)propionic acid



C₂₅ H₂₄ N₆ O₇ S; Mol wt: 552.5656

ACTION – Integrin antagonist with selectivity for $\alpha_v\beta_3$ (IC₅₀ = 0.81 nM) relative to $\alpha_v\beta_5$ (IC₅₀ > 10 μ M) and gpIIb/IIIa (IC₅₀ = 240 nM). Potentially useful in the treatment of osteoporosis, diabetic retinopathy, cancer and restenosis. Other exemplified compounds from this series of RGD mimetics containing a nitroaryl moiety include the following:



Compound	R1	R2	R3	A	Formula
285123	H	H	Ph	NH	C ₁₉ H ₂₃ N ₇ O ₇ S
285124	H	H	Ph	S	C ₁₉ H ₂₂ N ₆ O ₇ S ₂
285125	H	H	2-Naph	O	C ₂₃ H ₂₄ N ₆ O ₈ S
285126	H	H	2-Naph	NH	C ₂₃ H ₂₅ N ₇ O ₇ S
285127	-CH ₂ CH ₂ -		Ph	NH	C ₂₁ H ₂₅ N ₇ O ₇ S

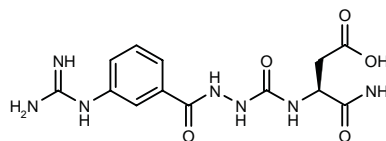
SOURCE – Scripps Research Institute, La Jolla, CA (US).

REFERENCES

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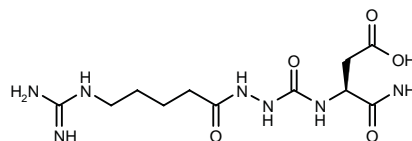
285466

N-[3-(3-Guanidinobenzoyl)carbazoyl]-L-aspartic acid 1-amide



C₁₃ H₁₇ N₇ O₅; Mol wt: 351.3213

ACTION – Integrin, particularly $\alpha_v\beta_3$ (vitronectin) receptor, antagonist, potentially useful in the treatment or prevention of osteoporosis, circulatory diseases, thrombosis, cardiac infarction, coronary heart disease, arteriosclerosis, angiogenesis and cancer. Another specifically claimed compound from this series of diacylhydrazine derivatives is:



285467: C₁₁ H₂₁ N₇ O₅

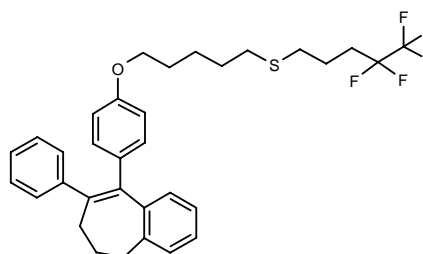
SOURCE – Merck KGaA.

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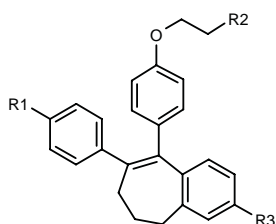
285580

9-[4-[5-(4,4,5,5,5-Pentafluoropentylsulfanyl)pentyloxy]-phenyl]-8-phenyl-6,7-dihydro-5*H*-benzocycloheptene



C₃₃ H₃₅ F₅ O S; Mol wt: 574.6945

ACTION – Agent for the treatment or prevention of osteoporosis that exhibits selective estrogenic activity on bones and is devoid of estrogenic activity on the uterus. Other specifically claimed compounds from this series of benzocycloheptenes include the following:



Compound	R1	R2	R3	Formula
285581	H	(CH2)3SOCH2CON(Me)Bu	H	C ₃₅ H ₄₃ NO ₃ S
285582	H	(CH2)3SOCH2CON(Me)Bu	OH	C ₃₅ H ₄₃ NO ₄ S
285584	OH	(CH2)3S(CH2)3CF2CF3	OH	C ₃₃ H ₃₅ F ₉ O ₃ S
285585	H	2-Pyr-CH2SO(CH2)3	OH	C ₃₄ H ₃₅ NO ₃ S
285586	H	NHCH2CH2OH	OH	C ₂₇ H ₂₉ NO ₃
285587	H	4-Me-PhCH2SO(CH2)3	OH	C ₃₆ H ₃₈ O ₃ S
285588	H	4-CF3-PhSO2(CH2)3	OH	C ₃₅ H ₃₃ F ₃ O ₄ S

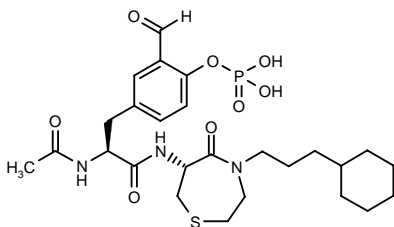
SOURCE – Schering AG.

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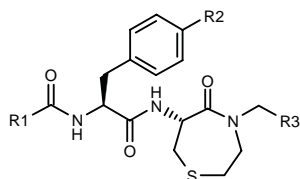
285713

*N*²-Acetyl-*N*¹-[4-(3-cyclohexylpropyl)-5-oxo-1,4-thiazepan-6(*R*)-yl]-3-formyl-4-*O*-phosphono-L-tyrosinamide

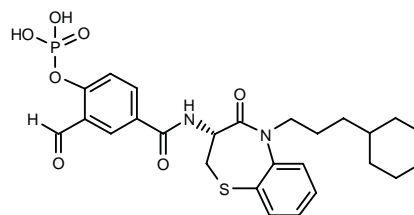


C26 H38 N3 O8 P S; Mol wt: 583.6392

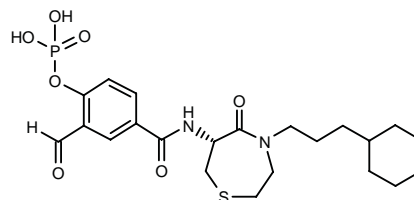
ACTION – Agent for the treatment of osteoporosis that acts as a human Src SH2 domain inhibitor, inhibiting osteoclast adhesion to bone and thus osteoclast-mediated bone resorption. Activity was demonstrated in a scintillation proximity assay (SPA) by its ability to inhibit ligand binding (IC₅₀ = 0.15 μmol). Other compounds from this series of thiazepinone derivatives include the following:



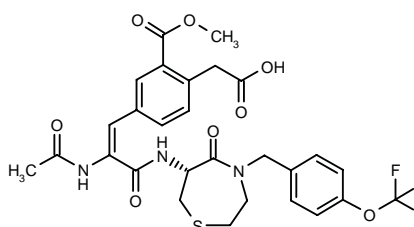
Compound	R1	R2	R3	Formula
285715	t-BuO	OPO3H2	cyclohexyl-CH2CH2	C ₂₈ H ₄₄ N ₃ O ₈ PS
285717	Me	CF2PO3H2	3-MeO-PhCH2CH2	C ₂₇ H ₃₄ F ₂ N ₃ O ₇ PS
285718	Me	CF2PO3H2	2-Naph	C ₂₈ H ₃₀ F ₂ N ₃ O ₆ PS
285719	Me	CF2PO3H2	4-(CF3O)-Ph	C ₂₈ H ₂₇ F ₃ N ₃ O ₇ PS
285721	Me	OPO3H2	CH2CH2SO2N(Me)Bu	C ₂₄ H ₃₉ N ₄ O ₉ PS ₂



285714: C26 H31 N2 O7 P S



285716: C22 H31 N2 O7 P S



285720: C28 H28 F3 N3 O8 S

SOURCE – Aventis Pharma.

REFERENCES

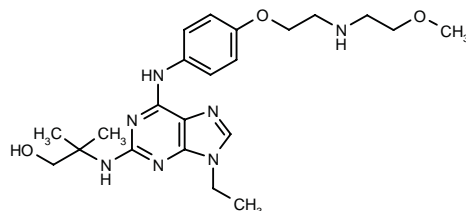
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NVP-AAK-980

281008

2-[9-Ethyl-6-[4-[2-(2-methoxyethylamino)ethoxy]-phenylamino]-9*H*-purin-2-ylamino]-2-methylpropan-1-ol

9-Ethyl-6-[4-[2-(2-methoxyethylamino)ethoxy]phenylamino]-2-(1,1-dimethyl-2-hydroxyethylamino)-9*H*-purine



C22 H33 N7 O3; Mol wt: 443.5487

ACTION – Potent tyrosine kinase Src inhibitor (IC_{50} = 3.3 nM against recombinant human enzyme) with high selectivity over other protein kinases including protein kinase C α (PKC- α) and Lck kinase, as well as against epidermal growth factor (EGF) receptor tyrosine kinase. Compound strongly inhibited Fak phosphorylation induced by Src in murine fibroblast cells (IC_{50} = 0.22 μ M) and, to a much lesser extent, that of Src itself by Csk (IC_{50} = 5.5 μ M). NVP-AAK-980 reduced thymidine incorporation in osteoblastic MC3T3-E1 cells stimulated by platelet-derived growth factor (PDGF; IC_{50} = 2.9 μ M) and it inhibited bone resorption induced by parathyroid hormone in organ cultures of fetal rat long bones (IC_{50} < 1 μ M). *In vivo*, a dose-dependent reduction in retinoid-induced hypercalcemia was observed in young thyroparathyroidectomized rats (ED_{50} = 30 mg/kg p.o.). Compound was well tolerated after 2 weeks of treatment at 25 mg/kg p.o. in female rats. Potentially useful for the treatment of osteoporosis and cancer-induced bone metastases.

SOURCE – Novartis.

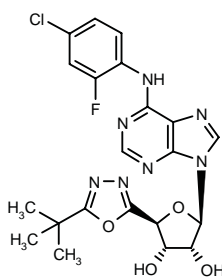
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2. Susa, M. and Teti, A. Tyrosine kinase Src inhibitors: Mechanisms of action in potential therapeutic applications. Drug News Perspect 2000, 13: in preparation.

TREATMENT OF LIPOPROTEIN DISORDERS

284944

2(S)-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-5(R)-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]tetrahydrofuran-3(S),4(R)-diol



C21 H21 Cl F N7 O4; Mol wt: 489.8929

ACTION – Potent and selective adenosine A_1 receptor agonist reported to possess antilipolytic properties and to reduce heart rate and conduction, with potential in the treatment of hyperlipidemia, diabetes, atherosclerosis, cardiac arrhythmias, angina, ischemic heart diseases, hypertension, heart failure, stroke, CNS disorders, sleep apnea and pain. Selectivity for A_1 receptors was demonstrated in a gene reporter assay, where compound exhibited ECR (equipotent concentration ratio relative to NECA = 1) values of 5.8 and 1066.71 for A_1 and A_3 receptors, respectively. A representative compound from a series of adenosine derivatives.

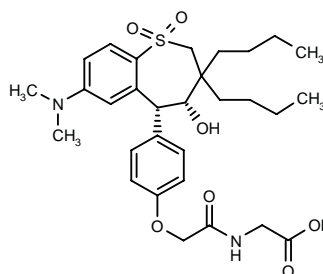
SOURCE – Glaxo Wellcome.

REFERENCES

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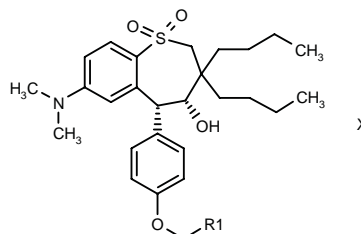
285663

2-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-4(R)-hydroxy-1,1-dioxo-2,3,4,5-tetrahydro-1-benzothiepin-5(R)-yl]-phenoxy]acetamido]acetic acid



C30 H42 N2 O7 S; Mol wt: 574.7348

ACTION – Agent for the treatment or prevention of hyperlipidemia, hypercholesterolemia and atherosclerosis that acts by inhibiting ileal bile acid transport and taurocholate uptake. Activity was demonstrated *in vivo* by a dose-dependent increase in fecal bile acid levels in rats when given at 0.08-2 mg/kg/day p.o. x 4 days. Other specifically claimed compounds within this series of benzothiepinines include the following:



Compound	R1	X ⁻	Formula
285664	4-(1-Pyr-CH2)-Ph	Cl ⁻	C ₃₉ H ₄₉ ClN ₂ O ₄ S
285665	4-(4-aza-1-azoniabicyclo-[2.2.2]oct-1-yl-CH2)-Ph	Cl ⁻	C ₄₀ H ₅₆ ClN ₃ O ₄ S
285666	4-[(CO2HCH2)2NCH2]-Ph		C ₃₈ H ₅₀ N ₂ O ₈ S
285667	6-(CO2HCH2CH2)-2-Pyr		C ₃₈ H ₄₆ N ₂ O ₆ S
285668	6-[(CO2HCH2)2NCH2]-2-Pyr		C ₃₇ H ₄₉ N ₃ O ₈ S

SOURCE – Pharmacia.

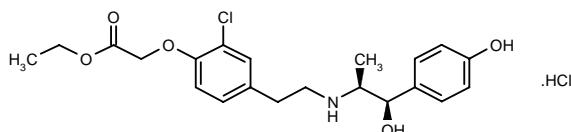
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TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

285287

2-[2-Chloro-4-[2-[2(*R*)-hydroxy-2-(4-hydroxyphenyl)-1(*S*)-methylethylamino]ethyl]phenoxy]acetic acid ethyl ester hydrochloride



C21 H26 Cl N O5 . HCl ; Mol wt: 444.3523

ACTION – Potent and selective β_3 -adrenoceptor agonist, as demonstrated in functional assays by EC_{50} values of 7.4 nM, 17 μ M and 0.52 μ M for stimulation of β_3 -adrenoceptors in ferret bladder smooth muscle, β_1 -adrenoceptors in rat atrium and β_2 -adrenoceptors in pregnant rat uterus, respectively. No mortality was observed following administration of 2 g/kg p.o. to rats. Potentially useful for the treatment or prevention of obesity, hyperglycemia, intestinal hypermotility, pollakiuria, urinary incontinence, depression, cholelithiasis and biliary tract hypermotility. A representative compound from a series of phenoxyacetic acid derivatives.

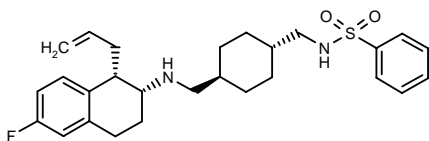
SOURCE – Kissei.

REFERENCES

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285373

(\pm)-*N*-[*trans*-4-(*cis*-1-Allyl-6-fluoro-1,2,3,4-tetrahydronaphthalen-2-ylaminomethyl)cyclohexylmethyl]-benzenesulfonamide



C27 H35 F N2 O2 S; Mol wt: 470.6495

ACTION – Potent neuropeptide Y (NPY) Y_5 receptor antagonist with high selectivity for the Y_5 receptor (IC_{50} = 21 nM against [125 I]-PYY binding to human NPY Y_5 receptors stably expressed in HEK293 cells) over Y_1 and Y_2 subtypes (IC_{50} > 10 μ M), G-protein-coupled receptors and ion channels. Compound showed good stability (95%) when incubated with human and rat S9 hepatic fractions. *In vivo*, at a dose of 30 mg/kg i.p. it was able to suppress food consumption in fasted rats (49% reduction 2 h after administration). Potentially useful for the treatment of eating disorders and obesity.

SOURCE – R.W. Johnson.

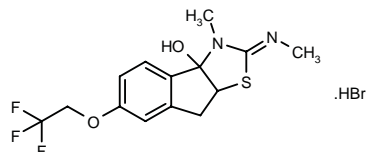
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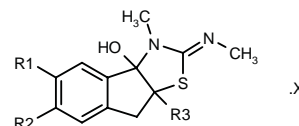
285589

3-Methyl-2-(methylimino)-6-(2,2,2-trifluoroethoxy)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]thiazol-3a-ol hydrobromide



C14 H15 F3 N2 O2 S . HBr; Mol wt: 413.2564

ACTION – Agent for the treatment or prevention of obesity and type II diabetes proven to decrease condensed milk consumption by 98% in fasted mice pretreated with 50 mg/kg p.o. Other compounds from this series of polycyclic thiazolidin-2-ylidene amines include the following:



Compound	R1	R2	R3	X	Isomer	Formula
285590	OCH2CF2CF2CF3	H	H	HCl		C ₁₆ H ₁₅ F ₇ N ₂ O ₂ S.HCl
285591	H	Cl	F		racemic	C ₁₂ H ₁₂ ClFN ₂ OS
285592	H	Cl	F	HCl	racemic	C ₁₂ H ₁₂ ClFN ₂ OS.HCl

SOURCE – Aventis Pharma.

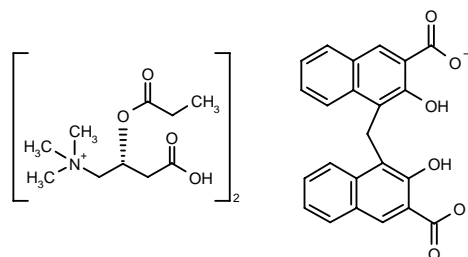
REFERENCES

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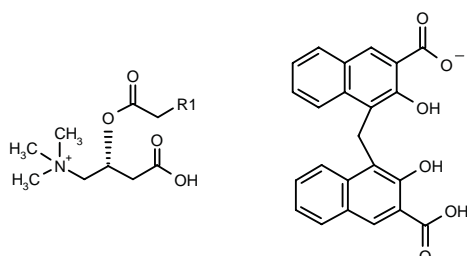
285658

4,4'-Methylenebis(3-hydroxynaphthalene-2-carboxylic acid) bis[*N*-[3-carboxy-2(*R*)-(propionyloxy)propyl]-*N,N,N*-trimethylammonium] salt

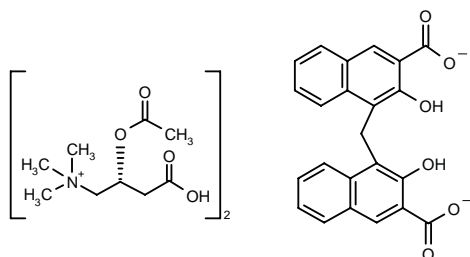


C23 H14 O6 . 2 C10 H20 N O4; Mol wt: 822.8996

ACTION – Nonhygroscopic salt of propionyl-L-carnitine reported to be suitable for the preparation of solid compositions for oral administration, particularly slow-release compositions. Other exemplified nonhygroscopic salts of L-carnitine and alkanoyl L-carnitine include the following:



Compound	R1	Formula
ST-1341 [285659]	Me	C ₃₃ H ₃₅ NO ₁₀
ST-1336 [285661]	H	C ₃₂ H ₃₃ NO ₁₀



ST-1335 [285660]: C₂₃ H₁₄ O₆ . 2 C₉ H₁₈ N O₄

SOURCE – Sigma-Tau.

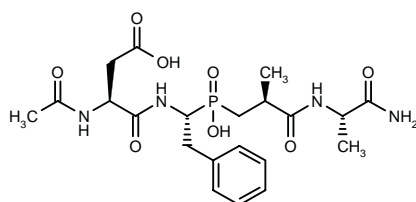
REFERENCES

1. Santaniello, M. et al. (Sigma-Tau Industrie Farmaceutiche Riunite SpA) *Solid compsns. suitable for oral administration containing non-hydroscopic salts of L-carnitine and alkanoyl L-carnitines*. WO 0001662.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

285053

3(S)-Acetamido-3-[N-[1(R)-[[2-[N-[1(S)-(carbamoyl)ethyl]-carbamoyl]propyl](hydroxy)phosphoryl]-2-phenylethyl]-carbamoyl]butyric acid



C₂₁ H₃₁ N₄ O₈ P; Mol wt: 498.4699

ACTION – A selective inhibitor of the N-terminal site of human angiotensin-converting enzyme (ACE), as demonstrated by a K_i value of 12 nM vs. 25 μM for the C-terminal site. *In vivo*, compound was shown to selectively inhibit the degradation of the peptide Ac-SDKP, which is known to regulate hematopoiesis, while having

no effect on renin levels, contrary to classical ACE inhibitors such as lisinopril, when given both at 10 mg/kg i.v. No toxicity was observed following administration of 25 mg/kg i.v. to mice. Potentially useful for protecting hematopoietic strain cells of patients subjected to aggressive chemotherapy or radiotherapy.

SOURCE – INSERM, Paris Cedex (FR).

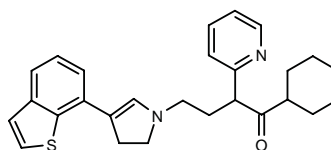
REFERENCES

1. Dive, V. et al. (Commissariat a l'Energie Atomique;INSERM [Institut National de la Sante et de la Recherche Medicale]) *N-Terminal site selective inhibitors of human angiotensin conversion enzyme (ACE)*. WO 0001706.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

284956

4-[4-(1-Benzothiophen-7-yl)-2,3-dihydro-1H-pyrrol-1-yl]-1-cyclohexyl-2-(2-pyridyl)-1-butanone



C₂₇ H₃₀ N₂ O S; Mol wt: 430.6130

ACTION – Combined 5-HT_{1A} and 5-HT_{2A} receptor antagonist and 5-HT reuptake inhibitor, potentially useful for alleviating tobacco or nicotine withdrawal symptoms, as well as for the treatment of anxiety, depression, hypertension, cognitive disorders, psychosis, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, eating disorders, substance abuse, obsessive-compulsive disorder, panic disorder and migraine. A representative compound from a series of pyrrolidine and pyrroline derivatives.

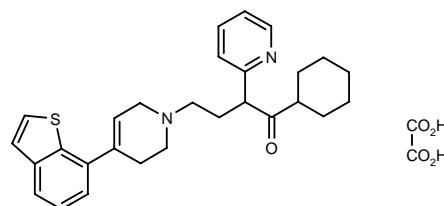
SOURCE – Lilly.

REFERENCES

1. Hertel, L.W. and Xu, Y.-C. (Eli Lilly and Company) *Pyrrolidine and pyrroline derivs. having effects on serotonin related systems*. WO 0000196.

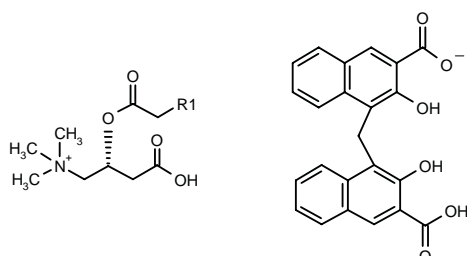
284957

4-[4-(1-Benzothiophen-7-yl)-1,2,3,6-tetrahydropyridin-1-yl]-1-cyclohexyl-2-(2-pyridyl)-1-butanone oxalate

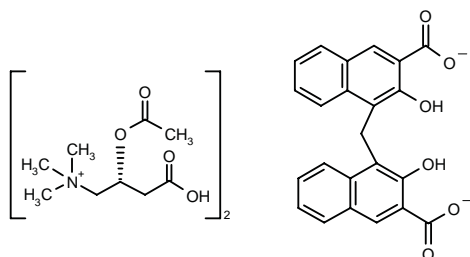


C₂₈ H₃₂ N₂ O S . C₂ H₂ O₄; Mol wt: 534.6736

ACTION – Nonhygroscopic salt of propionyl-L-carnitine reported to be suitable for the preparation of solid compositions for oral administration, particularly slow-release compositions. Other exemplified nonhygroscopic salts of L-carnitine and alkanoyl L-carnitine include the following:



Compound	R1	Formula
ST-1341 [285659]	Me	C ₃₃ H ₃₅ NO ₁₀
ST-1336 [285661]	H	C ₃₂ H ₃₃ NO ₁₀



ST-1335 [285660]: C₂₃ H₁₄ O₆ . 2 C₉ H₁₈ N O₄

SOURCE – Sigma-Tau.

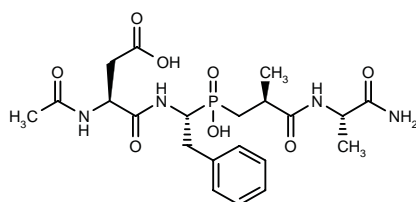
REFERENCES

1. Santaniello, M. et al. (Sigma-Tau Industrie Farmaceutiche Riunite SpA) *Solid compsns. suitable for oral administration containing non-hydroscopic salts of L-carnitine and alkanoyl L-carnitines*. WO 0001662.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

285053

3(S)-Acetamido-3-[N-[1(R)-[[2-[N-[1(S)-(carbamoyl)ethyl]-carbamoyl]propyl](hydroxy)phosphoryl]-2-phenylethyl]-carbamoyl]butyric acid



C₂₁ H₃₁ N₄ O₈ P; Mol wt: 498.4699

ACTION – A selective inhibitor of the N-terminal site of human angiotensin-converting enzyme (ACE), as demonstrated by a K_i value of 12 nM vs. 25 μM for the C-terminal site. *In vivo*, compound was shown to selectively inhibit the degradation of the peptide Ac-SDKP, which is known to regulate hematopoiesis, while having

no effect on renin levels, contrary to classical ACE inhibitors such as lisinopril, when given both at 10 mg/kg i.v. No toxicity was observed following administration of 25 mg/kg i.v. to mice. Potentially useful for protecting hematopoietic strain cells of patients subjected to aggressive chemotherapy or radiotherapy.

SOURCE – INSERM, Paris Cedex (FR).

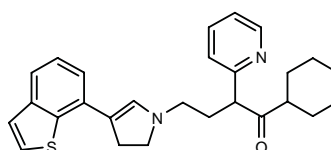
REFERENCES

1. Dive, V. et al. (Commissariat a l'Energie Atomique;INSERM [Institut National de la Sante et de la Recherche Medicale]) *N-Terminal site selective inhibitors of human angiotensin conversion enzyme (ACE)*. WO 0001706.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

284956

4-[4-(1-Benzothiophen-7-yl)-2,3-dihydro-1H-pyrrol-1-yl]-1-cyclohexyl-2-(2-pyridyl)-1-butanone



C₂₇ H₃₀ N₂ O S; Mol wt: 430.6130

ACTION – Combined 5-HT_{1A} and 5-HT_{2A} receptor antagonist and 5-HT reuptake inhibitor, potentially useful for alleviating tobacco or nicotine withdrawal symptoms, as well as for the treatment of anxiety, depression, hypertension, cognitive disorders, psychosis, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, eating disorders, substance abuse, obsessive-compulsive disorder, panic disorder and migraine. A representative compound from a series of pyrrolidine and pyrroline derivatives.

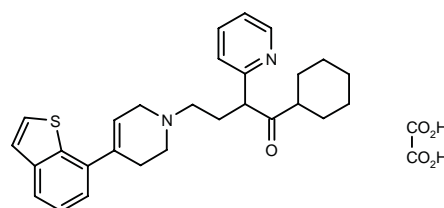
SOURCE – Lilly.

REFERENCES

1. Hertel, L.W. and Xu, Y.-C. (Eli Lilly and Company) *Pyrrolidine and pyrroline derivs. having effects on serotonin related systems*. WO 0000196.

284957

4-[4-(1-Benzothiophen-7-yl)-1,2,3,6-tetrahydropyridin-1-yl]-1-cyclohexyl-2-(2-pyridyl)-1-butanone oxalate



C₂₈ H₃₂ N₂ O S . C₂ H₂ O₄; Mol wt: 534.6736

ACTION – Combined 5-HT_{1A} and 5-HT_{2A} receptor antagonist and 5-HT reuptake inhibitor, potentially useful for alleviating tobacco or nicotine withdrawal symptoms, as well as for the treatment of anxiety, depression, hypertension, cognitive disorders, psychosis, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, eating disorders, substance abuse, obsessive-compulsive disorder, panic disorder and migraine. A representative compound from a series of piperidine derivatives.

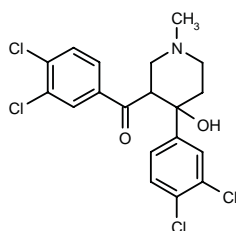
SOURCE – Lilly.

REFERENCES

1. Hertel, L.W. et al. (Eli Lilly and Company) *Piperidine derivs. having effects on serotonin related systems*. EP 0982304, WO 0000198.

285374

1-(3,4-Dichlorophenyl)-1-[4-(3,4-dichlorophenyl)-4-hydroxy-1-methylpiperidin-3-yl]methanone



C19 H17 Cl₄ N O₂; Mol wt: 433.1603

ACTION – Potent and highly selective dopamine transporter (DAT) inhibitor with 21-fold superior DAT binding affinity than cocaine ($K_i = 11$ and 231 nM, respectively, against [³H]-mazindol binding) and 5-fold greater potency for [³H]-dopamine reuptake inhibition ($IC_{50} = 51$ and 274 nM, respectively). Compound showed high selectivity over 5-HT and norepinephrine (NE) reuptake ($IC_{50} = 2380$ and 177 nM, respectively). In behavioral testing, compound (10-156 mg/kg i.p.) partially mimicked the effects of cocaine in increasing locomotor activity in mice, but it lacked cocaine-like discriminative stimulus effects in rats. Potentially useful for the treatment of cocaine abuse.

SOURCES – Georgetown University, Washington, DC (US); University of Texas Medical Branch at Galveston, Galveston, TX (US).

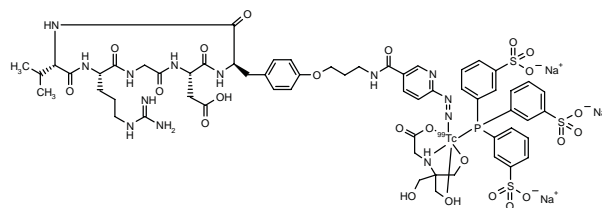
REFERENCES

1. Wang, S. et al. *Discovery of a novel dopamine transporter inhibitor, 4-hydroxy-1-methyl-4-(4-methylphenyl)-3-piperidyl 4-methylphenyl ketone, as a potential cocaine antagonist through 3D-database pharmacophore searching. Molecular modeling, structure-activity relationships, and behavioral pharmacological studies*. J Med Chem 2000, 43(3): 351.

DIAGNOSTIC AGENTS

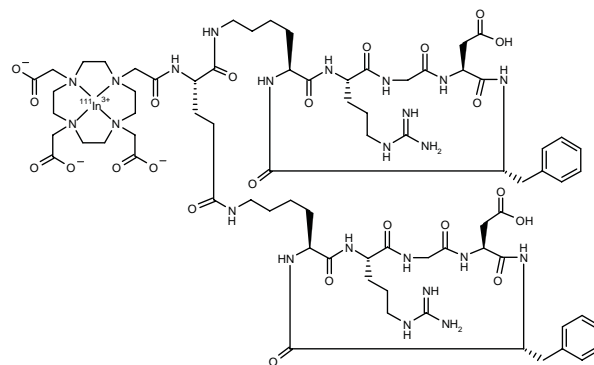
283170

Trisodium hydrogen [cyclo[L-arginyl-glycyl-L-aspartyl-4-O-[3-[6-(diazanyl-κN²)pyridin-3-ylcarboxamido]propyl]-D-tyrosyl-L-valylato(2-)]][N-[2-(hydroxy-κO)-1[(hydroxy-κO)methyl]-1-(hydroxymethyl)ethyl]glycinato(2-)-κN,κO]][[3,3',3''-(phosphinidyl-κP)tris(benzenesulfonato)](3-)]technetate(4-)-99Tc

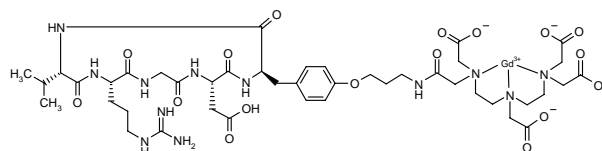


C59 H70 N13 Na3 O23 PS3 Tc; Mol wt: 1624.4120

ACTION – Imaging agent for the diagnosis and treatment of angiogenic disorders such as cancer, a specifically claimed compound from a series of derivatives consisting of a targeting moiety that binds to a receptor which is upregulated during angiogenesis, an operational linking group and a therapeutically effective radioisotope or diagnostically effective imageable moiety such as a gamma ray- or positron-emitting radioisotope, an MRI contrast agent, an X-ray contrast agent or an ultrasound contrast agent. Other specifically claimed compounds include the following:



283224: C75 H110 In N23 O23



283225: C43 H63 Gd N12 O17

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Rajopadhye, M. et al. (DuPont Pharmaceuticals Co.) *Pharmaceuticals for the imaging of angiogenic disorders*. WO 9958162.

ACTION – Combined 5-HT_{1A} and 5-HT_{2A} receptor antagonist and 5-HT reuptake inhibitor, potentially useful for alleviating tobacco or nicotine withdrawal symptoms, as well as for the treatment of anxiety, depression, hypertension, cognitive disorders, psychosis, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, eating disorders, substance abuse, obsessive-compulsive disorder, panic disorder and migraine. A representative compound from a series of piperidine derivatives.

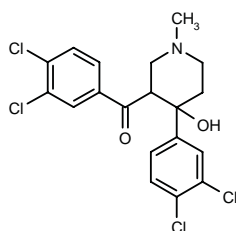
SOURCE – Lilly.

REFERENCES

1. Hertel, L.W. et al. (Eli Lilly and Company) *Piperidine derivs. having effects on serotonin related systems*. EP 0982304, WO 0000198.

285374

1-(3,4-Dichlorophenyl)-1-[4-(3,4-dichlorophenyl)-4-hydroxy-1-methylpiperidin-3-yl]methanone



C19 H17 Cl₄ N O₂; Mol wt: 433.1603

ACTION – Potent and highly selective dopamine transporter (DAT) inhibitor with 21-fold superior DAT binding affinity than cocaine ($K_i = 11$ and 231 nM, respectively, against [³H]-mazindol binding) and 5-fold greater potency for [³H]-dopamine reuptake inhibition ($IC_{50} = 51$ and 274 nM, respectively). Compound showed high selectivity over 5-HT and norepinephrine (NE) reuptake ($IC_{50} = 2380$ and 177 nM, respectively). In behavioral testing, compound (10-156 mg/kg i.p.) partially mimicked the effects of cocaine in increasing locomotor activity in mice, but it lacked cocaine-like discriminative stimulus effects in rats. Potentially useful for the treatment of cocaine abuse.

SOURCES – Georgetown University, Washington, DC (US); University of Texas Medical Branch at Galveston, Galveston, TX (US).

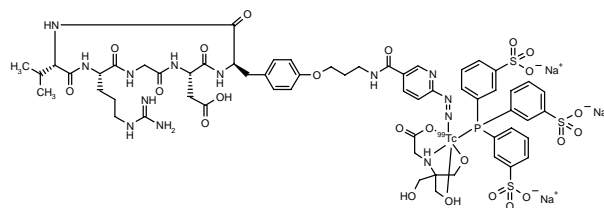
REFERENCES

1. Wang, S. et al. *Discovery of a novel dopamine transporter inhibitor, 4-hydroxy-1-methyl-4-(4-methylphenyl)-3-piperidyl 4-methylphenyl ketone, as a potential cocaine antagonist through 3D-database pharmacophore searching. Molecular modeling, structure-activity relationships, and behavioral pharmacological studies*. J Med Chem 2000, 43(3): 351.

DIAGNOSTIC AGENTS

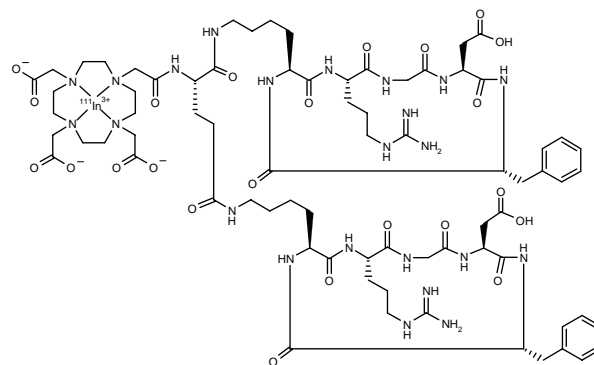
283170

Trisodium hydrogen [cyclo[L-arginyl-glycyl-L-aspartyl-4-*O*-[3-[6-(diazanyl-κN²)pyridin-3-ylcarboxamido]propyl]-D-tyrosyl-L-valylato(2-)]][N-[2-(hydroxy-κO)-1[(hydroxy-κO)methyl]-1-(hydroxymethyl)ethyl]glycinato(2-)-κN,κO]][[3,3',3''-(phosphinidyl-κP)tris(benzenesulfonato)](3-)]technetate(4-)-99Tc

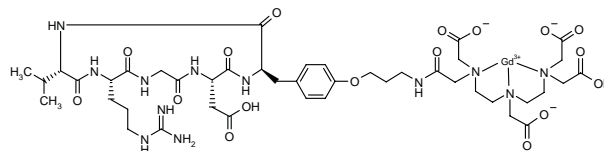


C59 H70 N13 Na3 O23 PS3 Tc; Mol wt: 1624.4120

ACTION – Imaging agent for the diagnosis and treatment of angiogenic disorders such as cancer, a specifically claimed compound from a series of derivatives consisting of a targeting moiety that binds to a receptor which is upregulated during angiogenesis, an operational linking group and a therapeutically effective radioisotope or diagnostically effective imageable moiety such as a gamma ray- or positron-emitting radioisotope, an MRI contrast agent, an X-ray contrast agent or an ultrasound contrast agent. Other specifically claimed compounds include the following:



283224: C75 H110 In N23 O23



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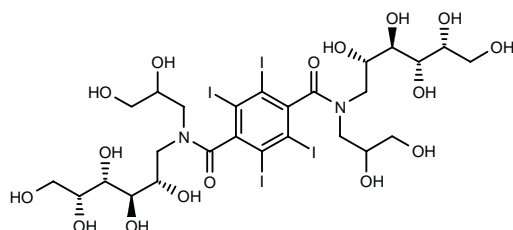
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Rajopadhye, M. et al. (DuPont Pharmaceuticals Co.) *Pharmaceuticals for the imaging of angiogenic disorders*. WO 9958162.

284925

*N*¹,*N*⁴-Bis(2,3-dihydroxypropyl)-2,3,5,6-tetraiodo-*N*¹,*N*⁴-bis[2(*S*),3(*R*),4(*S*),5(*R*),6-pentahydroxyhexyl]benzene-1,4-dicarboxamide



C₂₆ H₄₀ I₄ N₂ O₁₆; Mol wt: 1144.2000

ACTION – Contrast agent for use in X-ray radiology, particularly for visualizing the vascular compartment, nervous system, gastrointestinal tract, lung and kidneys.

SOURCE – Guerbet.

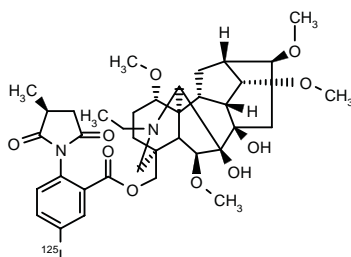
REFERENCES

1. Petta, M. (Guerbet SA) *Tetraiodoterephthalamide polyhydroxylated derivs., preparation method and use in radiology*. FR 2780287, WO 0000461.

[¹²⁵I]-Iodomethyllycaconitine**284283**

(1 α ,6 β ,14 α ,16 β)-20-Ethyl-4-[5-([¹²⁵I]iodo)-2-[3(*S*)-methyl-2,5-dioxypyrrolidin-1-yl]benzoyloxymethyl]-1,6,14,16-tetramethoxyaconitane-7,8-diol

[¹²⁵I]-Iodo-MLA



C₃₇ H₄₉ I N₂ O₁₀; Mol wt: 806.7981

ACTION – Iodinated nicotinic acetylcholine receptor (nAChR) α 7 ligand with high affinity (K_i = 1.6 nM) and selectivity relative to α 4 β 2 nAChRs (K_i > 1 μ M). Competition binding experiments using known α 7 nAChR ligands, α 4 β 2 nAChR agonists and antagonists and noncompetitive nAChR antagonists demonstrated the high specificity of the compound. Potentially useful as a radioligand for brain imaging in the diagnosis of Parkinson's disease, Alzheimer's disease and schizophrenia, as well as for studying the α 7 nAChR.

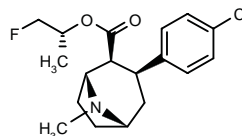
SOURCE – Research Triangle Institute, Research Triangle Park, NC (US).

REFERENCES

1. Navarro, H.A. et al. *Synthesis and pharmacological characterization of [¹²⁵I]iodomethyllycaconitine ([¹²⁵I]iodo-MLA). A new ligand for the α 7 nicotinic acetylcholine receptor*. J Med Chem 2000, 43(2): 142.

(*R*)-FIPCT**285010**

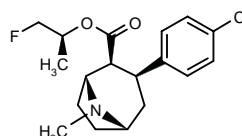
3*exo*-(4-Chlorophenyl)-8-methyl-8-azabicyclo[3.2.1]-octane-2*exo*-carboxylic acid 2-fluoro-1(*R*)-methylethyl ester



C₁₈ H₂₃ Cl F N O₂; Mol wt: 339.8357

Colorless microcrystalline solid, m.p. 98-9 °C.

ACTION – High-affinity dopamine (DA) transporter (DAT) ligand (K_i = 3.2 and 14.7 nM for human and rat DA transporter, respectively) with 20-fold selectivity over the human 5-HT transporter (K_i = 64 nM) and 33-fold selectivity over the rat norepinephrine (NE) transporter (K_i = 498 nM). Biodistribution studies in male rats demonstrated selective and specific uptake of the [¹⁸F]-labeled compound in the DA transporter-rich regions of the brain such as caudate and putamen. High drug uptake in these regions was confirmed in PET brain imaging studies in monkeys, in which caudate-to-cerebellum and putamen-to-cerebellum ratios were 2.5-3.5 at 115 min. The *in vivo* binding of fluorinated compound to the DA transporter in putamen and caudate was further demonstrated in rhesus monkeys by the absence of striatal radioactivity in the left hemisphere of monkeys previously given a left intracarotid artery infusion of the neurotoxin MPTP. Potentially useful as a radioligand for mapping the DAT complex in the human brain. The (*S*)-isomer is also potentially useful for mapping extrastriatal DAT sites and shows more prolonged retention than the (*R*)-isomer.



(*S*)-FIPCT [285011]: C₁₈ H₂₃ Cl F N O₂

SOURCE – Emory University, Atlanta, GA (US).

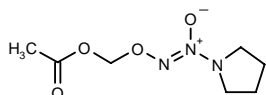
REFERENCES

1. Xing, D. et al. *Synthesis, biodistribution, and primate imaging of fluorine-18 labeled 2 β -carbo-1'-fluoro-2-propoxy-3 β -(4-chlorophenyl)tropanes. Ligands for the imaging of dopamine transporters by positron emission tomography*. J Med Chem 2000, 43(4): 639.

PHARMACOLOGICAL TOOLS

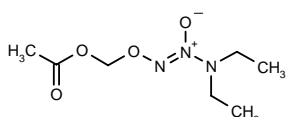
284932²

2-(Acetoxymethoxy)-1-(1-pyrrolidinyldiazen-1-ium-1-olate



C7 H13 N3 O4; Mol wt: 203.1967

ACTION – Antineoplastic agent, an esterase-sensitive nitric oxide (NO) donor prodrug proven to release large amounts of NO in the NO-sensitive human leukemia cell lines HL-60 and U973, where it exerted significant cytotoxic activity (IC_{50} = 6.4 and 53 μ M, respectively). In addition, the prodrug was able to induce apoptosis in both leukemia cell lines (> 75% apoptotic cells after 72-h incubation with 100 μ M). Compound showed limited suitability for *in vivo* application due to its rapid hydrolysis in rabbit blood, and is useful as a tool for probing the biological roles of NO. Another related compound is:



284931:^{1,2} C7 H15 N3 O4

SOURCE – National Cancer Institute, Bethesda, MD (US).

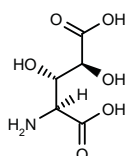
REFERENCES

1. Green, S.J. and Keefer, L.K. (Department of Health & Human Services;EntreMed, Inc.) *Encapsulated and non-encapsulated nitric oxide generators used as antimicrobial agents*. US 5814666.
2. Saavedra, J.E. et al. *Esterase-sensitive nitric oxide donors of the diazeniumdiolate family: In vitro antileukemic activity*. J Med Chem 2000, 43(2): 261.

285309

2(S)-Amino-3(S),4(S)-dihydroxypentanedioic acid

3(S),4(S)-Dihydroxy-L-glutamic acid



C5 H9 N O6; Mol wt: 179.1271

ACTION – Glutamic acid analogue with selective agonist activity at type 1 metabotropic glutamate receptors ($mGluR_1$ or $mglu_1$; EC_{50} = 257 μ M for stimulation of inositol phosphate production in HEK293 cells expressing $mGluR_1$) and weak antagonist activity at $mGluR_4$ ($mglu_4$). Potentially useful as a tool for studying the physiological role of the $mGluR_1$ subtype.

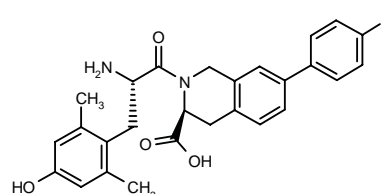
SOURCE – CNRS.

REFERENCES

1. Dauban, P. et al. *Application of 2,3-aziridino- γ -lactone methodology toward the enantiospecific synthesis of the (3S,4S) isomer of dihydroxy-L-glutamic acid*. Tetrahedron 1999, 55(24): 7589.
2. Dauban, P. et al. *First enantiospecific synthesis of a 3,4-dihydroxy-L-glutamic acid[(3S,4S)-DHGA], a new $mGluR1$ agonist*. Bioorg Med Chem Lett 2000, 10(2): 129.
3. Dodd, R.H. et al. *(3S,4S)-3,4-Dihydroxy-L-glutamic acid [(3S,4S)-DHGA]: A new $mGluR1$ agonist from 2,3-aziridino- γ -lactone*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 96.

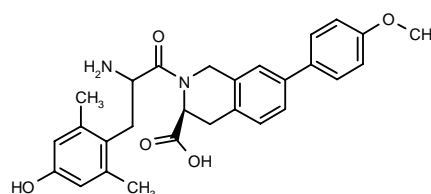
285314

2-[2(S)-Amino-3-(4-hydroxy-2,6-dimethylphenyl)propionyl]-7-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid



C27 H27 F N2 O4; Mol wt: 462.5183

ACTION – δ -Opioid receptor ligand with high affinity (IC_{50} = 3.8 nM) and good selectivity over μ - and κ -opioid receptors (IC_{50} = 587 and 7560 nM, respectively). In a functional assay *in vitro*, compound was able to block the effect of the selective δ -opioid receptor agonist SNC-80. Potentially useful as a pharmacological tool for elucidating the geometry of the opioid ligand-binding pocket. Another dipeptide analogue with a similar profile is:



285315: C28 H30 N2 O5

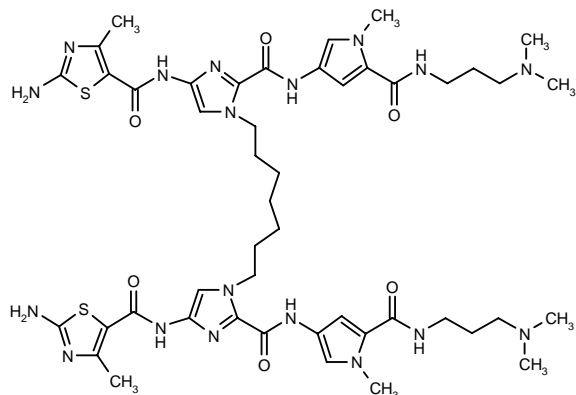
SOURCE – AstraZeneca.

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1. Pagé, D. et al. *Novel Dmt-Tic dipeptide analogues as selective delta-opioid receptor antagonists*. Bioorg Med Chem Lett 2000, 10(2): 167.

285785

1,1'-(Heptane-1,7-diyl)bis[4-(2-amino-4-methylthiazol-5-ylcarboxamido)-N-[2-[3-(dimethylamino)propyl-carbamoyl]-1-methylpyrrol-4-yl]imidazole-2-carboxamide]



C47 H66 N18 O6 S2; Mol wt: 1043.2900

ACTION – DNA gyrase inhibitor, a distamycin-related polyamide able to completely inhibit (at 0.5 μ M) the DNA supercoiling and cleavage reaction catalyzed by gyrase from *S. noursei*, with a potency superior to the naturally occurring parent compound.

SOURCE – University of Alberta, Edmonton, AB (CA).

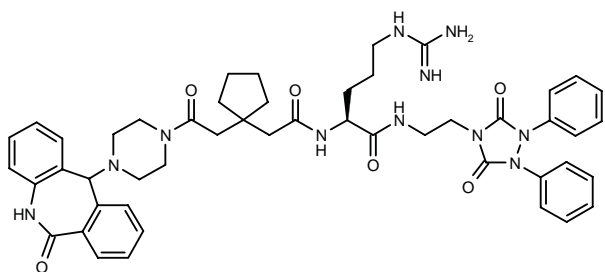
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- Sharma, S.K. et al. *Design and synthesis of novel thiazole-containing cross-linked polyamides related to the antiviral antibiotic distamycin*. J Org Chem 2000, 65(4): 1102.

BIIE-0246

285619

N-[1-[2-[4-(6-Oxo-6,11-dihydro-5H-dibenz[b,e]azepin-11-yl)-1-piperazinyl]cyclopentyl]acetyl]-L-arginine N-[2-(3,5-dioxo-1,2-diphenyl-1,2,3,4-tetrahydro-1,2,4-triazol-4-yl)ethyl]amide



C49 H57 N11 O6; Mol wt: 896.0603

ACTION – Selective and high-affinity, nonpeptide neuropeptide Y_2 receptor ligand ($IC_{50} = 3.3$ nM for inhibition of [125 I]-neuropeptide Y binding in human SMS-KAN cells), with high selectivity over Y_1 , Y_4 and Y_5 subtype receptors (inactive up 1 μ M); antagonist activity at the Y_2 receptor was demonstrated in electrically stimulated rat vas deferens ($K_b = 7.63$) but not at the Y_1 receptor in rabbit vas deferens (inactive up to 3 μ M). Potentially useful as a pharmacological tool to characterize the Y_2 receptor and to elucidate the pathophysiological role of this receptor.

SOURCE – Boehringer Ingelheim.

REFERENCES

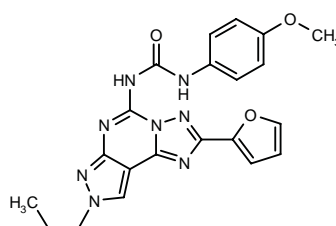
- Dollinger, H. et al. (Boehringer Ingelheim Pharma KG) *Novel subst. amino acid derivs., process for their preparation and pharmaceutical compns. containing them*. DE 19816929.
- Doods, H. et al. *BIIE0246: A selective and high affinity neuropeptide Y_2 receptor antagonist*. Eur J Pharmacol 1999, 384(2-3): R3.

MRE-3008-F20

282170

N-[2-(2-Furyl)-8-propyl-8H-pyrazolo[4,3-e][1,2,4]-triazolo[1,5-c]pyrimidin-5-yl]-N'-(4-methoxyphenyl)urea

MRE-3008



C21 H20 N8 O3; Mol wt: 432.4420

ACTION – High-affinity adenosine A_3 receptor ligand ($K_i = 0.29$ nM against [125 I]-AB-MECA binding to human receptors expressed in HEK293 cells) with high selectivity over rat A_1 and A_{2A} receptors ($K_i > 10,000$ and 1993 nM, respectively), as well as human A_1 and A_{2A} receptors ($K_i = 1197$ and 141 nM, respectively). Compound showed antagonist activity in a functional assay evaluating its ability to block the effect of IB-MECA on cAMP production in CHO cells ($IC_{50} = 4.5$ nM). The tritium-labeled compound was able to bind human adenosine A_3 receptors expressed in CHO cells with a K_D value of 0.82 nM and a B_{max} value of 297 fmol/mg protein and is the first high-affinity radioligand antagonist for these receptors. Potentially useful as a tool for characterizing A_3 receptors in both normal and pathological conditions.

SOURCE – Medco.

REFERENCES

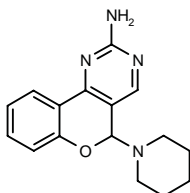
- Leung, E. (Medco Research Inc.) *The use of adenosine A_3 receptor antagonists to inhibit tumor growth*. WO 0010391.
- Baraldi, P.G. et al. *Pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine derivatives as highly potent and selective human A_3 adenosine receptor antagonists*. J Med Chem 1999, 42(22): 4473.
- Baraldi, P.G. et al. *Synthesis and preliminary biological evaluation of [3 H]-MRE 3008-F20: The first high affinity radioligand antagonist for the human A_3 adenosine receptors*. Bioorg Med Chem Lett 2000, 10(3): 209.
- Medco third quarter progress marked by initiation of phase II coronary diagnostic trial. DailyDrugNews.com (Daily Essentials) 1999, Oct 18.

ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

285996

5-(1-Piperidiny)-5*H*-1-benzopyran[4,3-*d*]pyrimidin-2-amine



C₁₆ H₁₈ N₄ O; Mol wt: 282.3452

ACTION – Antipyretic agent that prevents the febrile response caused by endotoxin in rats (ED_{50} = 9.7 mg/kg p.o.), with lesser analgesic (ED_{50} = 95 mg/kg p.o. against acetic acid-induced writhing in mice) and antiinflammatory activity (about 50% protection at 100 mg/kg p.o. in the carrageenan-induced paw edema assay). Compound did not exhibit ulcerogenic activity and showed gastro-protective activity, as demonstrated by its ability to prevent ethanol-induced gastric ulcers in rats. In addition, it was as effective as acetylsalicylic acid in inhibiting ADP-induced guinea pig platelet aggregation.

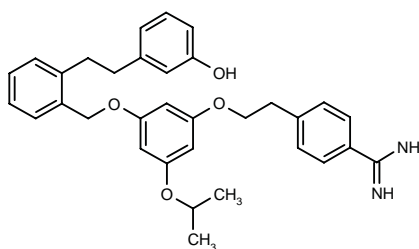
SOURCES – Università degli Studi di Genova, Genova (IT); Università degli Studi di Parma, Parma (IT).

REFERENCES

1. Bruno, O. et al. *Synthesis and pharmacological screening of novel non-acidic gastroprotective antipyretic anti-inflammatory agents with anti-platelet properties. 5-Alkyl/cycloalkylamino substituted 2-amino-5H-[1]benzopyrano[4,3-d]pyrimidines.* *Arzneim-Forsch Drug Res* 2000, 50(2): 140.

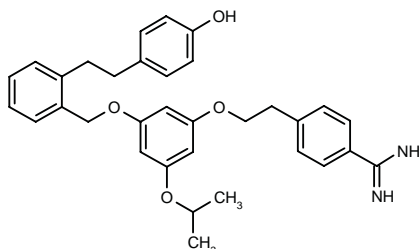
286079

4-[2-[3-[2-(3-Hydroxyphenyl)ethyl]benzyloxy]-5-(isopropoxy)phenoxy]ethyl]benzamidinium



C₃₃ H₃₆ N₂ O₄; Mol wt: 524.6574

ACTION – Calcium channel blocker, a nonpeptide analogue of the ω -conotoxin MVIIA, proven to block both N- and L-type voltage-sensitive calcium channels (IC_{50} = 2.7 and 3 μ M, respectively). A potential lead for the development of antinociceptive agents. Another related compound is:



286078: C₃₃ H₃₆ N₂ O₄

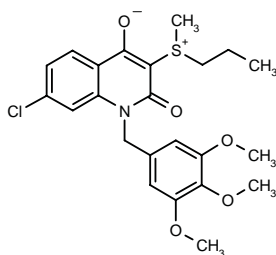
SOURCE – Warner-Lambert.

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1. Menzler, S. et al. *Design and biological evaluation of non-peptide analogues of ω -conotoxin MVIIA.* *Bioorg Med Chem Lett* 2000, 10(4): 345.

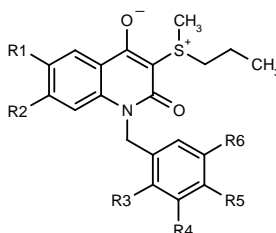
286230

7-Chloro-1-(3,4,5-trimethoxybenzyl)-3-[methyl(propyl)-sulfonio]-2-oxo-1,2-dihydroquinolin-4-olate



C23 H26 Cl N O5 S; Mol wt: 463.9794

ACTION – Analgesic agent proven active against substance P-induced pain in rats at 10 mg/kg p.o. A representative compound from a series of dihydroquinoline derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	R6	Formula
286231	H	Cl	H	H	OMe	H	C ₂₁ H ₂₂ ClNO ₃ S
286232	OMe	OMe	H	OMe	OMe	OMe	C ₂₅ H ₃₁ NO ₇ S
286233	OMe	OMe	H	H	OMe	H	C ₂₃ H ₂₇ NO ₅ S
286234	OMe	OMe	Cl	Cl	H	H	C ₂₂ H ₂₃ Cl ₂ NO ₄ S

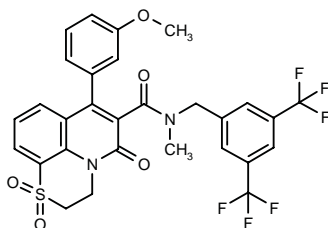
SOURCE – Otsuka.

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1. Shibuya, T. et al. (Otsuka Pharmaceutical Co., Ltd.) *Dihydroquinoline derivs.* JP 2000026424.

286259

N-[3,5-Bis(trifluoromethyl)benzyl]-*N*-methyl-7-(3-methoxyphenyl)-1,1,5-trioxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine



C29 H22 F6 N2 O5 S; Mol wt: 624.5558

ACTION – Tachykinin NK₁ (substance P) receptor antagonist, as shown in a functional assay in guinea pig ileum preparations, with potential in the treatment of urinary disorders, gastrointestinal disorders, emesis, migraine, asthma, rheumatoid arthritis and pain. A representative compound from a series of pyridobenzothiazine derivatives.

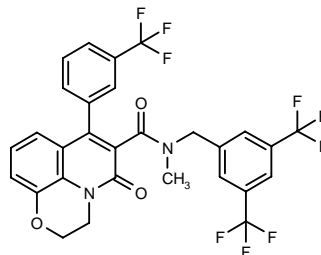
SOURCE – Kyorin.

REFERENCES

1. Fukuda, Y. et al. (Kyorin Pharmaceutical Co., Ltd.) *Pyridobenzothiazine derivs. and process for producing the same.* JP 2000103793, WO 0006580.

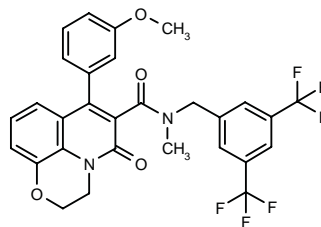
286260

N-[3,5-Bis(trifluoromethyl)benzyl]-*N*-methyl-5-oxo-7-[3-(trifluoromethyl)phenyl]-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxamide



C29 H19 F9 N2 O3; Mol wt: 614.4621

ACTION – Tachykinin, especially NK₁ (substance P), receptor antagonist, as demonstrated in a functional assay in guinea pig ileum preparations, with potential in the treatment of urinary disorders, gastrointestinal disorders, emesis, migraine, asthma, rheumatoid arthritis and pain. Another compound from this series of pyrido-benzoxazine derivatives is:



286261: C29 H22 F6 N2 O4

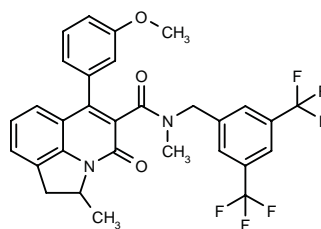
SOURCE – Kyorin.

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1. Fukuda, Y. et al. (Kyorin Pharmaceutical Co., Ltd.) *Pyridobenzoxazine derivs. and process for producing the same.* JP 2000103792, WO 0006578.

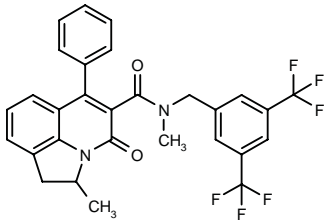
286278

N-[3,5-Bis(trifluoromethyl)benzyl]-6-(3-methoxyphenyl)-*N*,2-dimethyl-4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]-quinoline-5-carboxamide



C30 H24 F6 N2 O3; Mol wt: 574.5186

ACTION – Tachykinin NK₁ (substance P) receptor antagonist, as demonstrated in a functional assay in guinea pig ileum preparations, with potential in the treatment of urinary disorders, gastrointestinal disorders, emesis, migraine, asthma, rheumatoid arthritis and pain. Another compound from this series of pyrroloquinoline derivatives is:



286279: C29 H22 F6 N2 O2

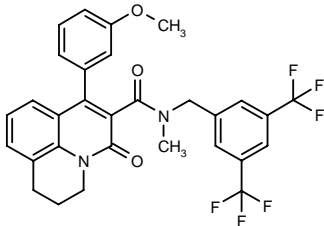
SOURCE – Kyorin.

REFERENCES

1. Fukuda, Y. and Tanioka, A. (Kyorin Pharmaceutical Co., Ltd.) *Pyrroloquinoline derivs. and process for producing the same*. JP 2000044561, WO 0006571.

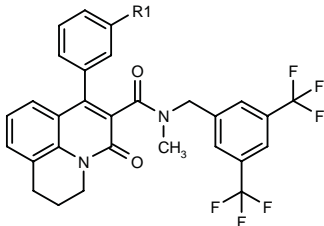
286280

N-[3,5-Bis(trifluoromethyl)benzyl]-7-(3-methoxyphenyl)-*N*-methyl-5-oxo-2,3-dihydro-1*H*,5*H*-benzo[*ij*]quinolizine-6-carboxamide



C30 H24 F6 N2 O3; Mol wt: 574.5186

ACTION – Tachykinin, particularly NK₁ (substance P), receptor antagonist, as demonstrated in a functional assay in guinea pig ileum preparations, with potential in the treatment of urinary disorders, gastrointestinal disorders, emesis, migraine, asthma, rheumatoid arthritis and pain. Other compounds from this series of benzoquinolizine derivatives include the following:



Compound	R1	Formula
286281	H	C ₂₉ H ₂₂ F ₆ N ₂ O ₂
286282	CF3	C ₃₀ H ₂₁ F ₉ N ₂ O ₂

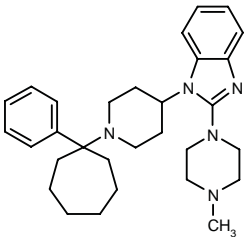
SOURCE – Kyorin.

REFERENCES

1. Fukuda, Y. and Tanioka, A. (Kyorin Pharmaceutical Co., Ltd.) *Benzoquinolizine derivs. and process for producing the same*. JP 2000044560, WO 0006572.

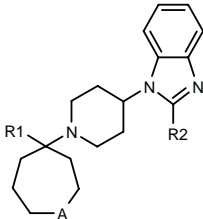
286484

2-(4-Methylpiperazin-1-yl)-1-[1-(1-phenylcycloheptyl)-piperidin-4-yl]-1*H*-benzimidazole



C30 H41 N5; Mol wt: 471.6889

ACTION – Selective ORL1 (N/OFQ) receptor agonist, potentially useful as an analgesic, antiinflammatory, diuretic, anesthetic, neuroprotective, antihypertensive and anxiolytic agent. Other specifically claimed compounds from this series of 2-substituted-1-piperidyl benzimidazole derivatives include the following:



Compound	R1	R2	R3	Formula
286485	Ph	NH2	-(CH2)3-	C ₂₇ H ₃₆ N ₄
286486	Me	NHMe	-(CH2)2-	C ₂₂ H ₃₄ N ₄
286487	Ph	NHCOCH2NH2	-CH2-	C ₂₇ H ₃₆ N ₅ O
286488	Ph	OCH2CH2NH2	-CH2-	C ₂₇ H ₃₆ N ₄ O
286489	Ph	SO2(CH2)3NH2	-CH2-	C ₂₈ H ₃₈ N ₄ O ₂ S
286490	Ph	NHCOCH2NH2	-(CH2)2-	C ₂₈ H ₃₇ N ₅ O

SOURCE – Pfizer.

REFERENCES

1. Ito, F. et al. (Pfizer Inc.) *2-Substd.-1-piperidyl benzimidazole cpds. as ORL1-receptor agonists*. WO 0008013.

HYPERIN

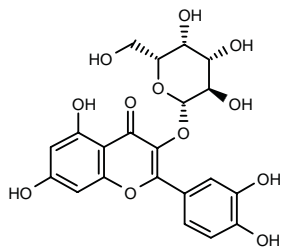
276716

2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-(β-D-galactopyranosyloxy)-4*H*-1-benzopyran-4-one

3,3',4,5,7-Pentahydroxyflavone 3-*O*-β-D-galactopyranoside

3-*O*-β-D-Galactopyranosylquercetin

Hyperoside



C21 H20 O12; Mol wt: 464.3770

ACTION – Nonopioid analgesic, a natural plant extract able to increase the pain threshold in several animal models including the hot-plate, writhing and tail-flick assays in mice. Compound appeared to act by blocking the activation of pain sensory afferent nerves by algescic factors, which appears to involve inhibition of the influx of calcium ions. Results of clinical trials demonstrated that locally applied compound attenuated both spontaneous and evoked pain in patients with oral ulcers, and this effect was sustained for up to 2 h. Toxicological studies indicate few side effects, with no evidence of tolerance, physical dependence or anesthesia.

SOURCE – Anhui Medical University, Hefei (CN).

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2. Chen, Z.W. et al. *Mechanism of analgesic action of hyperin.* Acta Pharm Sin 1989, 24: 326.

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8. Wang, W.Q. et al. *Protective effect of hyperin against myocardial ischemia and reperfusion injury.* Acta Pharmacol Sin 1996, 17: 341.

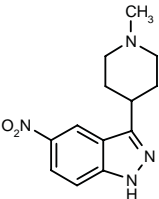
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MONOGRAPH – Wang, X.-W. et al. *Hyperin.* Drugs Fut 2000, 25(4): 0347.

ANTIMIGRAINE DRUGS

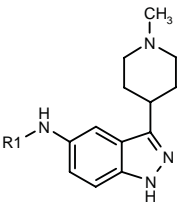
286194

3-(1-Methylpiperidin-4-yl)-5-nitro-1*H*-indazole



C13 H16 N4 O2; Mol wt: 260.2954

ACTION – 5-HT_{1f} receptor agonist with the ability to inhibit neuronal protein extravasation due to stimulation of the trigeminal ganglia and therefore useful for the treatment of migraine and associated disorders. Other exemplified compounds from this series of substituted indazole derivatives include the following:



Compound	R1	Formula
286195	H	C ₁₃ H ₁₈ N ₄
286196	4-F-PhCO	C ₂₀ H ₂₁ FN ₄ O

SOURCE – Lilly.

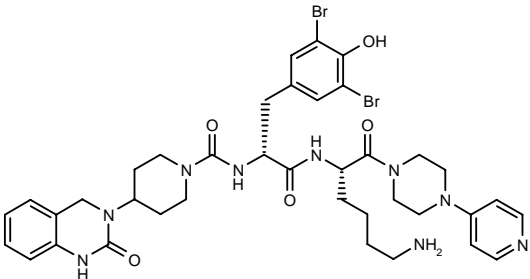
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1. Krushinski, J.H. Jr. and Schaus, J.M. (Eli Lilly and Company) *5-HT_{1F} agonists.* EP 0978514, WO 0006173.

BIBN-4096BS

285741

N-[2-[5-Amino-1(*S*)-[4-(4-pyridinyl)piperazin-1-yl]carbonyl]pentylamino]-1(*R*)-(3,5-dibromo-4-hydroxybenzyl)-2-oxoethyl]-4-(2-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)-piperidine-1-carboxamide



C38 H47 Br2 N9 O5; Mol wt: 869.6553

ACTION – Selective calcitonin gene-related peptide (CGRP) antagonist with subnanomolar affinity for the human CGRP receptor (K_i = 14.4 pM in human neuroblastoma SK-N-MC cells) and 236-fold selectivity over rat receptors (K_i = 3.4 nM in spleen cells). Compound displayed antagonist properties, with a pK_b value of 11 for antagonizing the CGRP-induced increase in cAMP levels in SK-N-MC cells. *In vivo*, it demonstrated strong inhibition of neurogenic vasodilatation; doses of 1-30 µg/kg i.v. were shown to inhibit the ipsilateral increase in facial blood flow induced by electrical stimulation of trigeminal ganglia in marmosets (50% inhibition at 3 µg/kg and complete blockade at 30 µg/kg). No cardiovascular effects were seen up to 1 mg/kg i.v. Compound is under clinical investigation for the acute treatment of migraine headache.

SOURCE – Boehringer Ingelheim.

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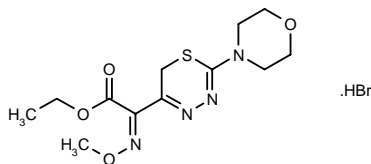
1. Rudolf, K. et al. (Dr. Karl Thomae GmbH) *Modified aminoacids, pharmaceuticals containing these cpds. and methods for their production.* WO 9811128.

2. Doods, H. et al. *Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist.* Br J Pharmacol 2000, 129(3): 420.

ANESTHETIC DRUGS

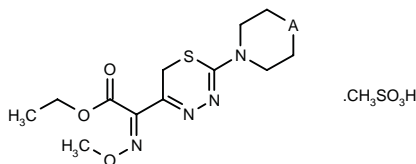
285863

2-(Methoxyimino)-2-[2-(4-morpholinyl)-6*H*-1,3,4-thiadiazin-5-yl]acetic acid ethyl ester hydrobromide



C12 H18 N4 O4 S . HBr; Mol wt: 395.2761

ACTION – Anesthetic agent with cardiovascular and hypometabolic activity, found to significantly reduce rectal temperature and oxygen consumption in mice at 390 mg/kg i.p. LD₅₀ = 830.5 mg/kg i.p. in mice. Compound is considered to be of value for use in complex surgical procedures or the treatment of life-threatening and/or traumatic situations such as stroke and myocardial infarction. Other compounds from this series of substituted 6*H*-1,3,4-thiadiazine-2-amines include the following:



Compound	A	Formula
285864	O	C ₁₂ H ₁₈ N ₄ O ₄ S.CH ₄ O ₃ S
285865	S	C ₁₂ H ₁₈ N ₄ O ₃ S ₂ .CH ₄ O ₃ S

SOURCE – Procter & Gamble.

REFERENCES

1. Chupakhin, O.N. et al. (The Procter & Gamble Co.) *Substd. 6H-1,3,4-thiadiazine-2-amines, the use thereof as anaesthetising, cardiovascular and hypometabolic agents, and a pharmaceutical compsn. containing them.* US 6028068, WO 9724353.

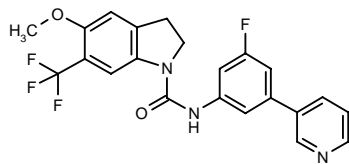
PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

SB-228357*

242325

N-[3-Fluoro-5-(3-pyridyl)phenyl]-5-methoxy-6-(trifluoromethyl)indoline-1-carboxamide



C22 H17 F4 N3 O2; Mol wt: 431.3930

ACTION – High-affinity ligand for the 5-HT_{2C} receptor (pK_i = 9.0) with 10-fold selectivity over 5-HT_{2B} (pK_i = 8.0) and more than 100-fold selectivity over 5-HT_{2A} receptors (pK_i = 6.9) and a panel of other receptors, ion channels and enzyme binding sites, that acts as an inverse agonist at this receptor. *In vivo*, compound was able to block the hypoactivity induced by the 5-HT_{2C} receptor agonist mCPP in rats (ID₅₀ = 0.7 mg/kg p.o.), exert significant anxiolytic activity in a conflict test and a social interaction test in rats at doses of 0.2-5 mg/kg p.o., and significantly reverse haloperidol-induced catalepsy in rats at doses of 0.32-10 mg/kg p.o. The acute administration of compound (up to 30 mg/kg p.o.) was not associated with pro-convulsant activity in the rat maximal electroshock seizure threshold model, and its chronic administration (30 mg/kg/day p.o. b.i.d. for 14 days) did not produce hyperphagia. Potentially useful as a nonsedating treatment for anxiety and depression, as well as other CNS disorders such as schizophrenia, migraine and Parkinson's disease.

SOURCE – SmithKline Beecham.

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2. Bromidge, S.M. (SmithKline Beecham plc) *Indole derivs. as 5-HT receptor antagonist.* EP 0891348, US 6028085, WO 9737989.

3. Gaster, L.M. et al. (SmithKline Beecham plc) *Indole derivs. as 5-HT receptor antagonist.* EP 0808312, JP 1998513442, US 5990133, WO 9623783.

4. Bromidge, S.M. et al. *Biarylcarbamoylindolines are novel and selective 5-HT_{2C} receptor inverse agonists: Identification of 5-methyl-1-[(2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]-6-trifluoromethylindoline (SB-243213) as a potential antidepressant/anxiolytic agent.* J Med Chem 2000, 43(6): 1123.

ACTION – Selective calcitonin gene-related peptide (CGRP) antagonist with subnanomolar affinity for the human CGRP receptor (K_i = 14.4 pM in human neuroblastoma SK-N-MC cells) and 236-fold selectivity over rat receptors (K_i = 3.4 nM in spleen cells). Compound displayed antagonist properties, with a pK_b value of 11 for antagonizing the CGRP-induced increase in cAMP levels in SK-N-MC cells. *In vivo*, it demonstrated strong inhibition of neurogenic vasodilatation; doses of 1-30 µg/kg i.v. were shown to inhibit the ipsilateral increase in facial blood flow induced by electrical stimulation of trigeminal ganglia in marmosets (50% inhibition at 3 µg/kg and complete blockade at 30 µg/kg). No cardiovascular effects were seen up to 1 mg/kg i.v. Compound is under clinical investigation for the acute treatment of migraine headache.

SOURCE – Boehringer Ingelheim.

REFERENCES

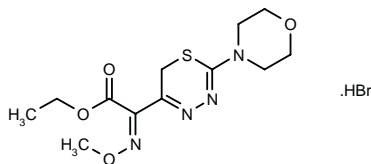
1. Rudolf, K. et al. (Dr. Karl Thomae GmbH) *Modified aminoacids, pharmaceuticals containing these cpds. and methods for their production.* WO 9811128.

2. Doods, H. et al. *Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist.* Br J Pharmacol 2000, 129(3): 420.

ANESTHETIC DRUGS

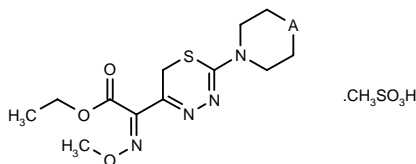
285863

2-(Methoxyimino)-2-[2-(4-morpholinyl)-6*H*-1,3,4-thiadiazin-5-yl]acetic acid ethyl ester hydrobromide



C12 H18 N4 O4 S . HBr; Mol wt: 395.2761

ACTION – Anesthetic agent with cardiovascular and hypometabolic activity, found to significantly reduce rectal temperature and oxygen consumption in mice at 390 mg/kg i.p. LD₅₀ = 830.5 mg/kg i.p. in mice. Compound is considered to be of value for use in complex surgical procedures or the treatment of life-threatening and/or traumatic situations such as stroke and myocardial infarction. Other compounds from this series of substituted 6*H*-1,3,4-thiadiazine-2-amines include the following:



Compound	A	Formula
285864	O	C ₁₂ H ₁₈ N ₄ O ₄ S·CH ₄ O ₃ S
285865	S	C ₁₂ H ₁₈ N ₄ O ₃ S ₂ ·CH ₄ O ₃ S

SOURCE – Procter & Gamble.

REFERENCES

1. Chupakhin, O.N. et al. (The Procter & Gamble Co.) *Substd. 6*H*-1,3,4-thiadiazine-2-amines, the use thereof as anaesthetising, cardiovascular and hypometabolic agents, and a pharmaceutical compsn. containing them.* US 6028068, WO 9724353.

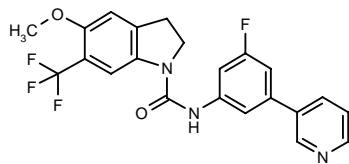
PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

SB-228357*

242325

N-[3-Fluoro-5-(3-pyridyl)phenyl]-5-methoxy-6-(trifluoromethyl)indoline-1-carboxamide



C22 H17 F4 N3 O2; Mol wt: 431.3930

ACTION – High-affinity ligand for the 5-HT_{2C} receptor (pK_i = 9.0) with 10-fold selectivity over 5-HT_{2B} (pK_i = 8.0) and more than 100-fold selectivity over 5-HT_{2A} receptors (pK_i = 6.9) and a panel of other receptors, ion channels and enzyme binding sites, that acts as an inverse agonist at this receptor. *In vivo*, compound was able to block the hypoactivity induced by the 5-HT_{2C} receptor agonist mCPP in rats (ID₅₀ = 0.7 mg/kg p.o.), exert significant anxiolytic activity in a conflict test and a social interaction test in rats at doses of 0.2-5 mg/kg p.o., and significantly reverse haloperidol-induced catalepsy in rats at doses of 0.32-10 mg/kg p.o. The acute administration of compound (up to 30 mg/kg p.o.) was not associated with pro-convulsant activity in the rat maximal electroshock seizure threshold model, and its chronic administration (30 mg/kg/day p.o. b.i.d. for 14 days) did not produce hyperphagia. Potentially useful as a nonsedating treatment for anxiety and depression, as well as other CNS disorders such as schizophrenia, migraine and Parkinson's disease.

SOURCE – SmithKline Beecham.

REFERENCES

1. Blackburn, T.P. (SmithKline Beecham plc) *Pharmaceutical compsn. containing a 5HT_{2C} antagonist and a D₂ antagonist.* WO 9804289.

2. Bromidge, S.M. (SmithKline Beecham plc) *Indole derivs. as 5-HT receptor antagonist.* EP 0891348, US 6028085, WO 9737989.

3. Gaster, L.M. et al. (SmithKline Beecham plc) *Indole derivs. as 5-HT receptor antagonist.* EP 0808312, JP 1998513442, US 5990133, WO 9623783.

4. Bromidge, S.M. et al. *Biarylcarbamoylindolines are novel and selective 5-HT_{2C} receptor inverse agonists: Identification of 5-methyl-1-[(2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]-6-trifluoromethylindoline (SB-243213) as a potential antidepressant/anxiolytic agent.* J Med Chem 2000, 43(6): 1123.

5. Reavill, C. et al. *5-HT_{2C} receptor antagonists, but not a 5-HT_{2A} or 5-HT_{2B} receptor antagonist, attenuate haloperidol-induced catalepsy in rat.* Br J Pharmacol 1998, 125(Suppl.): Abst 65P.

6. Reavill, C. et al. *Attenuation of haloperidol-induced catalepsy by a 5-HT_{2C} receptor antagonist.* Br J Pharmacol 1999, 126(3): 572.

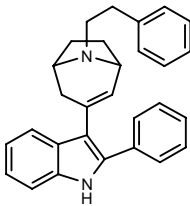
7. SmithKline Beecham Annual Report 1996.

*Identified compound **242325** (see **240933**) Drug Data Rep 1996, 018(11): 0959.

ANTIPSYCHOTIC DRUGS

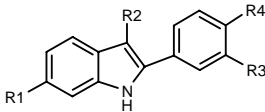
285482

2-Phenyl-3-[8-(2-phenylethyl)-8-azabicyclo[3.2.1]oct-2-en-3-yl]-1*H*-indole



C29 H28 N2; Mol wt: 404.5542

ACTION – Agent for the treatment or prevention of CNS disorders, particularly schizophrenia, a potent and selective 5-HT_{2A} receptor antagonist (K_i = 100 nM or less against [³H]-ketanserin binding to the human receptor cloned in CHO cells). Other specifically claimed compounds from this series of azabicycle-substituted phenylindole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
285483	F	8-azabicyclo[3.2.1]oct-2-en-3-yl	H	H	C ₂₁ H ₁₉ FN ₂
285484	H	8-azabicyclo[3.2.1]oct-2-en-3-yl	-OCH2O-	H	C ₂₂ H ₂₀ N ₂ O ₂
285485	H	9-Me-9-azabicyclo-[3.3.1]non-2-en-3-yl	H	H	C ₂₃ H ₂₄ N ₂
285486	H	endo-8-(3-thienyl-CH2CH2)-8-azabicyclo[3.2.1]oct-3-yl	H	H	C ₂₇ H ₂₈ N ₂ S

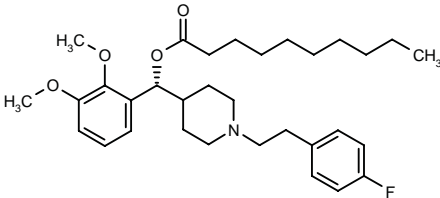
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Goodacre, S.C. et al. (Merck Sharp & Dohme Ltd.) *Azabicycle-substd. phenylindole derivs. as ligands for 5-HT_{2A} receptors.* WO 0004017.

286026

(+)-Decanoic acid 1(*R*)-(2,3-dimethoxyphenyl)-1-[1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl]methyl ester



C32 H46 F N O4; Mol wt: 527.7164

ACTION – Novel ester prodrug of the known 5-HT_{2A} receptor antagonist MDL-100907⁺ with potential in the treatment of schizophrenia, obsessive–compulsive disorder, drug addiction, depressive disorders including bipolar depression, anxiety, coronary vasospasm, angina and thrombotic disorders. Its efficacy was tested *in vivo* by its ability to antagonize DOI-induced behavior in rats, exhibiting significant activity for 28 days after a single dose equivalent to 120 mg/kg MDL-100907 by i.m. injection. A representative compound from a series of ester derivatives of MDL-100907.

SOURCE – Aventis Pharma.

REFERENCES

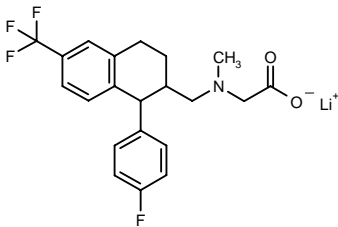
1. Carr, A.A. et al. (Aventis Pharmaceuticals Inc.) *Esters of (+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol and their use as prodrugs of the 5HT_{2A} receptor antagonist MDL 100,907.* WO 0021930.

2. Carr, A.A. et al. (Aventis Pharmaceuticals Inc.) *Esters of (+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol.* US 6028083.

*Drug Data Rep 1992, 014(10): 0858.

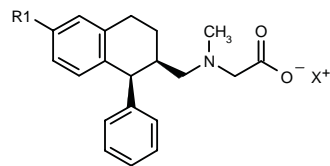
286382

(–)-2-[*N*-[1-(4-Fluorophenyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-2-ylmethyl]-*N*-methylamino]acetic acid lithium salt



C21 H20 F4 Li N O2; Mol wt: 401.3270

ACTION – Selective inhibitor of the glycine GlyT-1b transporter as compared to the GlyT-2 transporter, giving a pIC₅₀ value of 7.3 in the glycine uptake assay in CHO cells expressing the human GlyT-1b transporter. Potentially useful in the treatment or prevention of schizophrenia, depression, dementia and other types of cognitive impairment, neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease and Huntington’s disease, or muscle hyperactivity associated with spasticity, myoclonus and epilepsy. Other specifically claimed aminomethylcarboxylic acid derivatives are:



Compound	R1	X ⁺	Formula
286383	OMe	Li ⁺	C ₂₁ H ₂₄ LiNO ₃
286389	Me	Na ⁺	C ₂₁ H ₂₄ NNaO ₂
286391	OPh	Na ⁺	C ₂₆ H ₂₆ NNaO ₃
286393	t-BuCH2O	Li ⁺	C ₂₅ H ₃₂ LiNO ₃

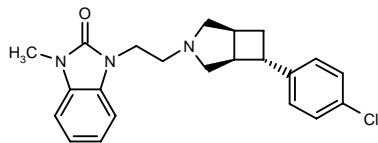
SOURCE – Akzo Nobel.

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1. Gibson, S.G. et al. (Akzo Nobel N.V.) *Aminomethylcarboxylic acid derivs.* WO 0007978.

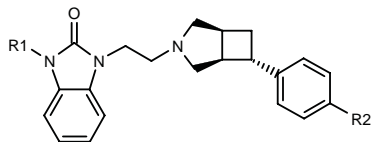
286470

(+)-1-[2-[(1*S*,5*R*,6*S*)-6-(4-Chlorophenyl)-3-azabicyclo[3.2.0]hept-3-yl]ethyl]-3-methyl-2,3-dihydro-1*H*-benzimidazol-2-one



C22 H24 Cl N3 O; Mol wt: 381.9046

ACTION – Agent with high affinity and selectivity for dopamine D₄ and 5-HT_{2A} receptors and reported to be devoid of cardiotoxicity (prolongation of the Q-T interval), contrary to structurally related compounds. Potentially useful as an atypical antipsychotic, antidepressant, sedative, hypnotic and neuroprotective agent and for the treatment of cocaine dependency. Other compounds from this series of *N*-substituted azabicycloheptane derivatives include the following:



Compound	R1	R2	Formula
286471	Et	Cl	C ₂₃ H ₂₆ ClN ₃ O
286472	cyclopropyl	F	C ₂₄ H ₂₆ FN ₃ O

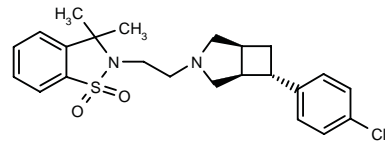
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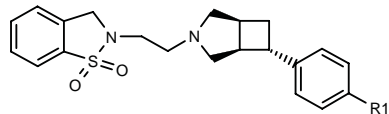
286473

(+)-2-[2-[(1*S*,5*R*,6*S*)-6-(4-Chlorophenyl)-3-azabicyclo[3.2.0]hept-3-yl]ethyl]-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide



C23 H27 Cl N2 O2 S; Mol wt: 430.9973

ACTION – Agent with high affinity and selectivity for dopamine D₄ and 5-HT_{2A} receptors and reported to be devoid of cardiotoxicity (prolongation of the Q-T interval), contrary to structurally related compounds. Potentially useful as an atypical antipsychotic, antidepressant, sedative, hypnotic and neuroprotective agent and for the treatment of cocaine dependency. Other compounds from this series of *N*-substituted azabicycloheptane derivatives include the following:



Compound	R1	Formula
286474	Cl	C ₂₁ H ₂₃ ClN ₂ O ₂ S
286475	F	C ₂₁ H ₂₃ FN ₂ O ₂ S

SOURCE – BASF.

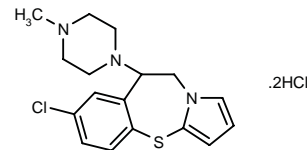
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ST-1469

286188

(+)-7-Chloro-9-(4-methylpiperazin-1-yl)-9,10-dihydro-pyrrolo[2,1-*b*][1,3]benzothiazepine dihydrochloride



C17 H20 Cl N3 S . 2HCl; Mol wt: 406.8068

ACTION – Atypical antipsychotic agent possessing improved affinity for dopamine and 5-HT_{2A} receptors compared to clozapine and olanzapine. Furthermore, the compound presented lower affinity for D₂ receptors (K_i = 49.60 nM), involved in extrapyramidal side effects, when compared to its close structural analogue *R*-(-)-octoclohepin, together with improved affinity for 5-HT₂ (K_i = 1.48 nM) and D₁ receptors (K_i = 16.40 nM), involved in neuroleptic effects, when compared to olanzapine. *In vivo* evaluation of ST-1469 demonstrated its ability to inhibit apomorphine-induced climbing in mice (ED₅₀ = 0.10 mg/kg s.c.) and 5-MeO-DMT-induced head twitches in mice (ED₅₀ = 0.196 mg/kg s.c.), while having no cataleptogenic effect in rats at doses up to 12.2 mg/kg s.c.

SOURCE – Sigma-Tau.

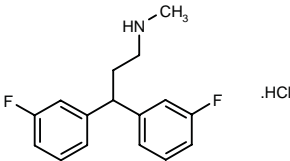
REFERENCES

1. Campiani, G. et al. (Sigma-Tau Industrie Farmaceutiche Riunite SpA) *Pyrrolo[2,1-b]-[1,3]benzothiazepines with atypical antipsychotic activity*. WO 0006579.

TREATMENT OF MOOD DISORDERS

285766

N-[3,3-Bis(3-fluorophenyl)propyl]-*N*-methylamine hydrochloride



C16 H17 F2 N . HCl; Mol wt: 297.7742

ACTION – Agent for the treatment of CNS disorders, particularly depression, a combined 5-HT reuptake inhibitor and NMDA receptor antagonist. *In vitro*, compound exhibited K_i values of 0.068, > 10.0 and 0.914 μ M for inhibition of 5-HT, norepinephrine and dopamine reuptake, respectively. In addition, it gave an IC_{50} value of 0.416 μ M for inhibition of NMDA receptor-mediated increases in cytosolic calcium in cultured rat cerebellar granule cells and an IC_{50} value of 0.641 μ M for displacement of [3 H]-MK-801 binding from NMDA receptors in rat cortex. Antidepressant activity was demonstrated in the forced swimming test in mice and rats at 5 mg/kg p.o.

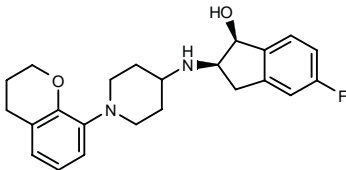
SOURCE – NPS Pharmaceuticals.

REFERENCES

1. Mueller, A. et al. (NPS Pharmaceuticals, Inc.) *Methods and cpds. for treating depression and other disorders*. WO 0002551.

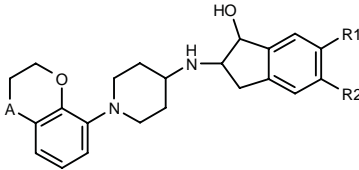
286528

cis-2-[1-(3,4-Dihydro-2*H*-1-benzopyran-8-yl)piperidin-4-ylamino]-5-fluoroindan-1-ol



C23 H27 F N2 O2; Mol wt: 382.4763

ACTION – Potent and selective 5-HT_{1B} receptor ligand with very good affinity for guinea pig brain 5-HT_{1B} receptors, giving pK_i values of over 7.4 in a binding assay, as well as low affinity for 5-HT_{1A} receptors, with pK_i values of about 6. Such a profile is expected to be of use in the treatment of psychiatric disorders such as depression, anxiety, panic attacks, schizophrenia and obsessive–compulsive disorder, neurodegenerative disorders such as Parkinson’s disease and Alzheimer’s disease, pain, migraine, stroke, bulimia, anorexia, drug abuse and cardiovascular disorders such as unstable angina. Other indan-1-ol derivatives include the following:



Compound	R1	R2	A	Isomer	Formula
286530	H	F	CH2	trans	C ₂₃ H ₂₇ FN ₂ O ₂
286531	H	H	O	cis	C ₂₂ H ₂₆ N ₂ O ₃
286532	H	H	O	trans	C ₂₂ H ₂₆ N ₂ O ₃
286534	F	H	CH2	cis	C ₂₃ H ₂₇ FN ₂ O ₂
286535	F	H	CH2	trans	C ₂₃ H ₂₇ FN ₂ O ₂
286537	Me	H	O	cis	C ₂₃ H ₂₈ N ₂ O ₃
286538	Me	H	O	trans	C ₂₃ H ₂₈ N ₂ O ₃
286539	-OCH2O-		CH2	cis	C ₂₄ H ₂₈ N ₂ O ₄
286541	-OCH2O-		CH2	trans	C ₂₄ H ₂₈ N ₂ O ₄

SOURCE – ADIR.

REFERENCES

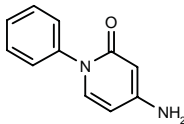
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

286351

4-Amino-1-phenylpyridin-2(1*H*)-one



C11 H10 N2 O; Mol wt: 186.2130

ACTION – Anticonvulsant with ED₅₀ values in the maximal electroshock seizure (MES) and rotarod (neurotoxicity) tests in mice of 3.1 and 200 mg/kg p.o., respectively. Other specifically claimed compounds from this series of 4-amino-1-aryl-pyridin-2-ones include the following:

SOURCE – Sigma-Tau.

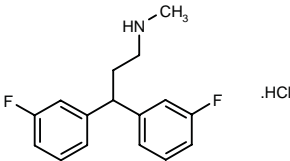
REFERENCES

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TREATMENT OF MOOD DISORDERS

285766

N-[3,3-Bis(3-fluorophenyl)propyl]-*N*-methylamine hydrochloride



C16 H17 F2 N . HCl; Mol wt: 297.7742

ACTION – Agent for the treatment of CNS disorders, particularly depression, a combined 5-HT reuptake inhibitor and NMDA receptor antagonist. *In vitro*, compound exhibited K_i values of 0.068, > 10.0 and 0.914 μ M for inhibition of 5-HT, norepinephrine and dopamine reuptake, respectively. In addition, it gave an IC_{50} value of 0.416 μ M for inhibition of NMDA receptor-mediated increases in cytosolic calcium in cultured rat cerebellar granule cells and an IC_{50} value of 0.641 μ M for displacement of [3 H]-MK-801 binding from NMDA receptors in rat cortex. Antidepressant activity was demonstrated in the forced swimming test in mice and rats at 5 mg/kg p.o.

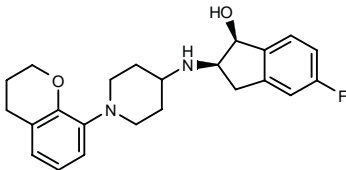
SOURCE – NPS Pharmaceuticals.

REFERENCES

1. Mueller, A. et al. (NPS Pharmaceuticals, Inc.) *Methods and cpds. for treating depression and other disorders*. WO 0002551.

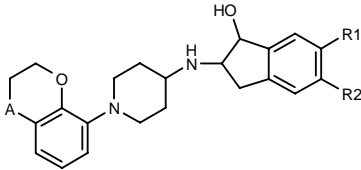
286528

cis-2-[1-(3,4-Dihydro-2*H*-1-benzopyran-8-yl)piperidin-4-ylamino]-5-fluoroindan-1-ol



C23 H27 F N2 O2; Mol wt: 382.4763

ACTION – Potent and selective 5-HT_{1B} receptor ligand with very good affinity for guinea pig brain 5-HT_{1B} receptors, giving pK_i values of over 7.4 in a binding assay, as well as low affinity for 5-HT_{1A} receptors, with pK_i values of about 6. Such a profile is expected to be of use in the treatment of psychiatric disorders such as depression, anxiety, panic attacks, schizophrenia and obsessive–compulsive disorder, neurodegenerative disorders such as Parkinson’s disease and Alzheimer’s disease, pain, migraine, stroke, bulimia, anorexia, drug abuse and cardiovascular disorders such as unstable angina. Other indan-1-ol derivatives include the following:



Compound	R1	R2	A	Isomer	Formula
286530	H	F	CH2	trans	C ₂₃ H ₂₇ FN ₂ O ₂
286531	H	H	O	cis	C ₂₂ H ₂₆ N ₂ O ₃
286532	H	H	O	trans	C ₂₂ H ₂₆ N ₂ O ₃
286534	F	H	CH2	cis	C ₂₃ H ₂₇ FN ₂ O ₂
286535	F	H	CH2	trans	C ₂₃ H ₂₇ FN ₂ O ₂
286537	Me	H	O	cis	C ₂₃ H ₂₈ N ₂ O ₃
286538	Me	H	O	trans	C ₂₃ H ₂₈ N ₂ O ₃
286539	-OCH2O-		CH2	cis	C ₂₄ H ₂₈ N ₂ O ₄
286541	-OCH2O-		CH2	trans	C ₂₄ H ₂₈ N ₂ O ₄

SOURCE – ADIR.

REFERENCES

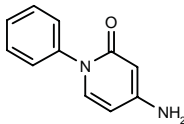
1. Peglion, J.-L. et al. (ADIR et Cie.) *Indane-1-ol derivs., process for their preparation and pharmaceutical compsns. containing them*. EP 0982305, FR 2782515, JP 2000072748.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

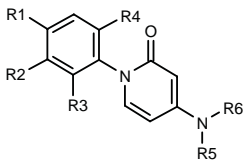
286351

4-Amino-1-phenylpyridin-2(1*H*)-one



C11 H10 N2 O; Mol wt: 186.2130

ACTION – Anticonvulsant with ED₅₀ values in the maximal electroshock seizure (MES) and rotarod (neurotoxicity) tests in mice of 3.1 and 200 mg/kg p.o., respectively. Other specifically claimed compounds from this series of 4-amino-1-aryl-pyridin-2-ones include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
286352	H	H	Cl	H	H	H	C ₁₁ H ₉ ClN ₂ O
286353	Cl	H	H	H	H	H	C ₁₁ H ₉ ClN ₂ O
286354	H	H	Me	H	H	H	C ₁₂ H ₁₂ N ₂ O
286355	H	Me	H	H	H	H	C ₁₂ H ₁₂ N ₂ O
286356	Me	H	H	H	H	H	C ₁₂ H ₁₂ N ₂ O
286357	OMe	H	H	H	H	H	C ₁₂ H ₁₂ N ₂ O ₂
286358	OCF ₃	H	H	H	H	H	C ₁₂ H ₉ F ₃ N ₂ O ₂
286359	H	H	Cl	Cl	H	H	C ₁₁ H ₈ Cl ₂ N ₂ O
286360	H	H	F	H	H	H	C ₁₁ H ₉ FN ₂ O
286361	F	H	H	H	H	H	C ₁₁ H ₉ FN ₂ O
286362	H	H	F	F	H	H	C ₁₁ H ₈ F ₂ N ₂ O
286363	F	H	Cl	H	H	H	C ₁₁ H ₈ ClFN ₂ O
286364	H	H	Cl	H	Me	Me	C ₁₃ H ₁₃ ClN ₂ O
286365	H	H	Cl	H	-CH ₂ CH ₂ OCH ₂ CH ₂ -		C ₁₅ H ₁₅ ClN ₂ O ₂

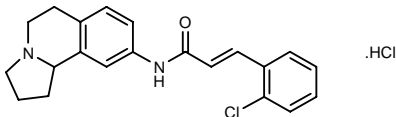
SOURCE – Arzneimittelwerk Dresden.

REFERENCES

1. Lankau, H.-J. et al. (Arzneimittelwerk Dresden GmbH) *New 4-amino-1-aryl-pyridine-2-ones with anticonvulsive action and method for producing same*. DE 19835918, WO 0007988.

286397

3-(2-Chlorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)-2(E)-propenamide hydrochloride



C21 H21 Cl N2 O . HCl; Mol wt: 389.3238

ACTION – Anticonvulsant with high affinity for the receptor site labeled by [³H]-SB-204269 (pK_i = 8.6 in rat forebrain tissue), proven active *in vivo* in the maximal electroshock seizure (MES) test in rats, where it produced a 432% increase in seizure threshold at 1 h after a dose of 2 mg/kg p.o. Potentially useful in the treatment or prevention of epilepsy and other CNS and neurological disorders including anxiety, depression, withdrawal from substances of abuse, Parkinson’s disease, Alzheimer’s disease, migraine, schizophrenia and motor neuron diseases. A representative compound from a series of condensed tricyclic piperidines.

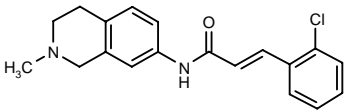
SOURCE – SmithKline Beecham.

REFERENCES

1. Novelli, R. and Porter, R.A. (SmithKline Beecham plc) *Condensed tricyclic piperidines having anti-convulsant activity*. WO 0008023.

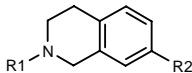
286406

3-(2-Chlorophenyl)-N-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2(E)-propenamide



C19 H19 Cl N2 O; Mol wt: 326.8251

ACTION – Anticonvulsant with affinity for the receptor site labeled by [³H]-SB-204269 (pK_i > 7.5 in rat forebrain tissue), proven active *in vivo* in the maximal electroshock seizure (MES) test in rats, where it produced a 245% increase in seizure threshold at 1 h after a dose of 10 mg/kg p.o. Potentially useful in the treatment or prevention of epilepsy and other CNS and neurological disorders including anxiety, depression, withdrawal from substances of abuse, Parkinson’s disease, Alzheimer’s disease, migraine, schizophrenia and motor neuron diseases. Other compounds from this series of tetrahydroiso-quinolinyl cinnamides and acrylamides include the following:



Compound	R1	R2	Formula
286407	Me	2-Cl-6-F-PhCH=CHCONH	C ₁₉ H ₁₈ ClFN ₂ O
286408	H	CH=CHCONHPh	C ₁₈ H ₁₈ N ₂ O

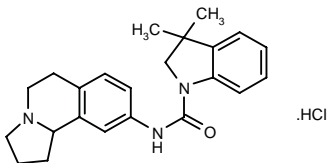
SOURCE – SmithKline Beecham.

REFERENCES

1. Coulton, S. et al. (SmithKline Beecham plc) *Substd. isoquinoleines and their use as anticonvulsivants*. WO 0007993.

286415

N-(1,2,3,5,6,10b-Hexahydropyrrolo[2,1-a]isoquinolin-9-yl)-3,3-dimethyl-2,3-dihydro-1H-indole-1-carboxamide hydrochloride



C23 H27 N3 O . HCl; Mol wt: 397.9472

ACTION – Anticonvulsant that binds to the receptor site in rat forebrain labeled by [³H]-SB-204269 with a pK_i value > 8.5. In addition, the compound elevated the seizure threshold in the maximal electroshock seizure (MES) test in rats by 410% at a dose of 2 mg/kg p.o. Potentially useful in the treatment of epilepsy, anxiety, depression, withdrawal from substances of abuse, Parkinson’s disease, psychosis, migraine, cerebral ischemia, Alzheimer’s disease, sleep disorders, neuropathic pain, multiple sclerosis and amyotrophic lateral sclerosis.

SOURCE – SmithKline Beecham.

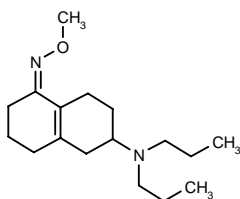
REFERENCES

1. Coulton, S. and Porter, R.A. (SmithKline Beecham plc) *Urea derivs.* WO 0008022.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

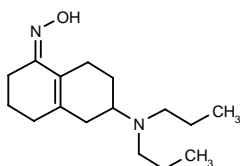
286144

(±)-6-(Dipropylamino)-1,2,3,4,5,6,7,8-octahydronaphthalen-1-one *O*-methyloxime



C17 H30 N2 O; Mol wt: 278.4370

ACTION – Agent for the treatment of Parkinson's disease with good dopamine D₁ and D₂ receptor-agonist activity *in vivo*. Dopamine-agonist activity was demonstrated by its ability to induce contralateral rotations in 6-OHDA-lesioned rats following oral doses of 1 and 3 mg. In addition, compound was shown to reverse the increase in L-DOPA induced by γ -butyrolactone and NSD-1015 in striatum and mesolimbic regions of rats treated with 3 μ g/kg p.o. by 70 and 56%, respectively, thus showing that it acts as an agonist at presynaptic dopamine receptors in these regions of the brain. Another specifically claimed compound from this series of hexahydro-naphthalenone oximes and hydrazones is:



286145: C16 H28 N2 O

SOURCE – Warner-Lambert.

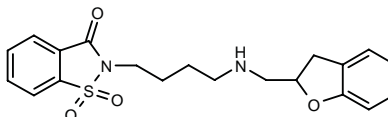
REFERENCES

1. Johnson, S.J. et al. (Warner-Lambert Co.) *Hexahydro-naphthalenone oximes and hydrazones.* WO 0006536.

TREATMENT OF NAUSEA AND VOMITING

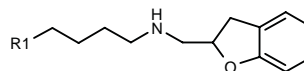
285855

2-[4-(2,3-Dihydrobenzofuran-2-ylmethylamino)butyl]-2,3-dihydro-1,2-benzisothiazole-1,1,3-trione

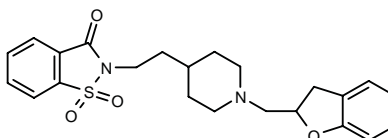


C20 H22 N2 O4 S; Mol wt: 386.4698

ACTION – Agent with high affinity for 5-HT_{1A} receptors (K_i = 2.3 nM in rat hippocampal membranes) and α_1 -adrenoceptors (K_i = 31 nM in rat cortical preparations), proven to exert antiemetic activity in a ferret model at 3 mg/kg i.p. Potentially useful in the treatment of nausea and vomiting, anxiety, depression, eating disorders and hypertension. Other compounds from this series of 2,3-dihydrobenzofuran derivatives include the following:



Compound	R1	Formula
285857	1,3-dioxo-2-isindoliny	C ₂₁ H ₂₂ N ₂ O ₃
285858	7,9-dioxo-8-azaspiro[4.5]dec-8-yl	C ₂₂ H ₃₀ N ₂ O ₃
285859	2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl	C ₂₁ H ₂₂ N ₂ O ₄



285860: C23 H26 N2 O4 S

SOURCE – Asahi Chemical.

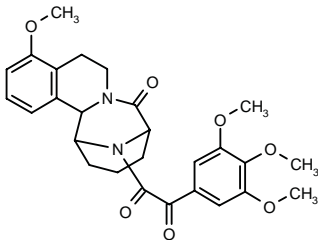
REFERENCES

1. Ogami, Y. and Mochizuki, D. (Asahi Chemical Industry Co., Ltd.) *2,3-Dihydrobenzofuran derivs.* JP 2000007671.

COGNITION-ENHANCING DRUGS

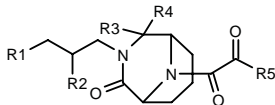
285593

1-(8-Methoxy-4-oxo-2,3,4,6,7,11b-hexahydro-1*H*-1,3-propenopyrazino[2,1-*a*]isoquinolin-2-yl)-2-(3,4,5-trimethoxyphenyl)-1,2-ethanedione

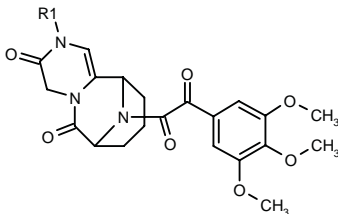


C27 H30 N2 O7; Mol wt: 494.5410

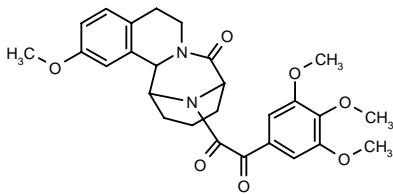
ACTION – Neurotrophic agent that acts by inhibiting rotamase (peptidylprolyl isomerase) activity associated with the FK-506-binding protein FKBP-12 (K_i app = 0.027 μ M), resulting in stimulation of neurite outgrowth. Compound is reported to be devoid of immunosuppressive activity. Potentially useful for promoting the repair of neuronal damage caused by disease or physical trauma, e.g., Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis. Other compounds from this series of bicyclic [3.3.1], [4.3.1] or polycyclic azaamide derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
285594	H	CH2Ph	-O-		3,4,5-(MeO)3-Ph	C ₂₈ H ₃₂ N ₂ O ₇
285596	OCOCH(allyl)2	(S)-OCH2-Ph	H	H	3,4,5-(MeO)3-Ph	C ₃₈ H ₄₄ N ₂ O ₉
285597	OCOCH(allyl)2	(R)-OCH2-Ph	H	H	1-(MeOCH2CO2-CH2)-1-cyclopentyl	C ₃₈ H ₄₈ N ₂ O ₉
285598	OCOCH(allyl)2	(R)-OCH2-Ph	H	H	1-(AcOCH2)-1-cyclopentyl	C ₃₅ H ₄₆ N ₂ O ₈
285675	OCOCH(allyl)2	(S)-OCH2-Ph	H	H	1-(MeOCH2CO2-CH2)-1-cyclopentyl	C ₃₈ H ₄₈ N ₂ O ₉



Compound	R1	Formula
285599	cyclopentyl	C ₂₈ H ₃₁ N ₃ O ₇
285600	3,5-(MeO)2-Ph	C ₂₉ H ₃₁ N ₃ O ₉



285595: C27 H30 N2 O7

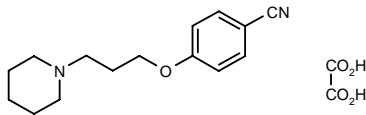
SOURCE – Agouron (Warner-Lambert).

REFERENCES

1. Kato, S. et al. (Agouron Pharmaceuticals, Inc.) *Cpds., compsns., and methods for stimulating neuronal growth and elongation*. WO 0004020.

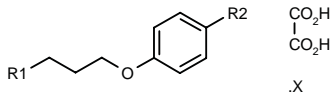
285641

4-[3-(1-Piperidinyl)propoxy]benzonitrile oxalate



C15 H20 N2 O . C2 H2 O4; Mol wt: 334.3698

ACTION – Histamine H₃ receptor antagonist expected to be devoid of the problems associated with imidazole-containing prior art compounds such as poor blood–brain barrier penetration and/or hepatic or ocular toxicity. Its activity was assessed by measuring the increase in *tele*-methylhistamine levels in the brain of mice (ED₅₀ = 0.20 mg/kg p.o.). Potentially useful in the treatment of CNS disorders such as Alzheimer’s disease, mood and attention disorders, cognitive deficits, obesity, vertigo and motion sickness. Other compounds from this series of aryloxy- or arylthio-alkylamines include the following:



Compound	R1	R2	X	Formula
285642	1-pyrrolidinyl-CH2CH2	NO2		C ₁₅ H ₂₂ N ₂ O ₃ ·C ₂ H ₂ O ₄
285643	N(Et)2	CN		C ₁₄ H ₂₀ N ₂ O·C ₂ H ₂ O ₄
285644	N(Et)2	Ac		C ₁₅ H ₂₃ NO ₂ ·C ₂ H ₂ O ₄
285645	1-pyrrolidinyl-CH2CH2	CH(OH)Me		C ₁₇ H ₂₇ NO ₂ ·C ₂ H ₂ O ₄
285646	CH2N(Et)2	CN		C ₁₅ H ₂₂ N ₂ O·C ₂ H ₂ O ₄
285647	hexahydro-1-azepinyl	CN		C ₁₆ H ₂₂ N ₂ O·C ₂ H ₂ O ₄
285648	N(Et)2	CH(OH)Me	H2O	C ₁₅ H ₂₅ NO ₂ ·C ₂ H ₂ O ₄ ·H ₂ O
285649	N(Et)2	C(Me)=NOH		C ₁₅ H ₂₄ N ₂ O ₂ ·C ₂ H ₂ O ₄
285650	3-Me-1-Pip	Ac		C ₁₇ H ₂₅ NO ₂ ·C ₂ H ₂ O ₄
285651	4-Me-1-Pip	Ac		C ₁₇ H ₂₅ NO ₂ ·C ₂ H ₂ O ₄
285652	1-Pip	COEt		C ₁₇ H ₂₅ NO ₂ ·C ₂ H ₂ O ₄

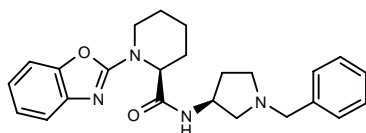
SOURCE – Bioprojet.

REFERENCES

1. Schwartz, J.-C. et al. (Societe Civile Bioprojet) *Non-imidazole aryloxy (or arylthio) alkylamines as histamine H₃-receptor antagonists and their therapeutic applications*. EP 0978512.

285672

1-(Benzoxazol-2-yl)-*N*-[1-benzylpyrrolidin-3(*S*)-yl]piperidine-2(*S*)-carboxamide



C₂₄ H₂₈ N₄ O₂; Mol wt: 404.5112

ACTION – An inhibitor of rotamase (peptidylprolyl isomerase) activity of FKBP (FK-506-binding protein)-type immunophilins, particularly FKBP-12 (IC₅₀ < 1200 nM) and FKBP-52 (IC₅₀ = 2790 nM); compound does not significantly inhibit the protein phosphatase calcineurin and is therefore devoid of significant immunosuppressive activity. Potentially useful for promoting neuronal regeneration and outgrowth and for the treatment of neurological disorders arising from neurodegenerative diseases or other disorders involving nerve damage such as senile dementia and other dementias, amyotrophic lateral sclerosis and other motor neuron diseases, Parkinson's disease, Huntington's disease, neurological deficits associated with stroke, spinal cord injury, peripheral neuropathy, multiple sclerosis and hearing disorders such as tinnitus.

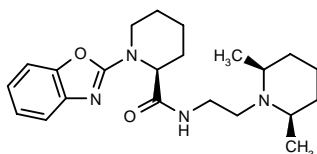
SOURCE – Pfizer.

REFERENCES

1. Kemp, M.I. et al. (Pfizer Ltd.;Pfizer Inc.) *Heterocyclic cpds. as inhibitors of rotamase enzymes*. WO 0005232.

285686

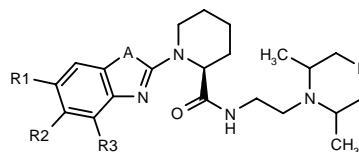
1-(Benzoxazol-2-yl)-*N*-[2-(*cis*-2,6-dimethylpiperidin-1-yl)-ethyl]piperidine-2(*S*)-carboxamide



C₂₂ H₃₂ N₄ O₂; Mol wt: 384.5208

ACTION – An inhibitor of rotamase (peptidylprolyl isomerase) activity of FKBP (FK-506-binding protein)-type immunophilins, particularly FKBP-12 and FKBP-52, that does not significantly inhibit the protein phosphatase calcineurin and is therefore devoid of significant immunosuppressive activity. Potentially useful for promoting neuronal regeneration and outgrowth and for the treatment of neurological disorders arising from neurodegenerative diseases or other disorders involving nerve damage, such as senile dementia and other

dementias, amyotrophic lateral sclerosis and other motor neuron diseases, Parkinson's disease, Huntington's disease, neurological deficits associated with stroke, spinal cord injury, peripheral neuropathy, multiple sclerosis and hearing disorders such as tinnitus. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	B	Isomer	Formula
285687	H	H	H	O	N(CONH-i-Pr)	cis	C ₂₅ H ₃₈ N ₆ O ₃
285688	H	H	H	O	O		C ₂₁ H ₃₀ N ₄ O ₃
285689	H	H	H	NH	CH ₂	cis	C ₂₂ H ₃₃ N ₅ O
285690	H	OMe	H	NH	CH ₂	cis	C ₂₃ H ₃₅ N ₅ O ₂
285691	F	H	H	NH	CH ₂	cis	C ₂₂ H ₃₂ N ₅ O
285692	H	H	Me	NH	CH ₂	cis	C ₂₃ H ₃₅ N ₅ O
285693	Me	Me	H	O	CH ₂	cis	C ₂₄ H ₃₆ N ₄ O ₂

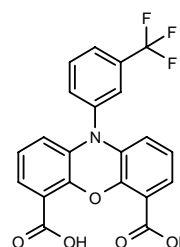
SOURCE – Pfizer.

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1. Wythes, M.J. et al. (Pfizer Inc.;Pfizer Ltd.) *FKBP inhibitors*. WO 0005231.

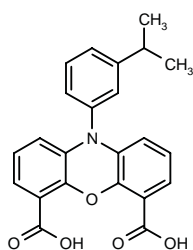
285723

10-[3-(Trifluoromethyl)phenyl]-10*H*-phenoxazine-4,6-dicarboxylic acid



C₂₁ H₁₂ F₃ N O₅; Mol wt: 415.3218

ACTION – Small-molecule transthyretin (TTR) amyloid fibril inhibitor proven to strongly inhibit both wild-type TTR and the L55P variant at 3.6 and 7.2 μM, respectively, with similar binding affinity for and inhibition of wild-type TTR as flufenamic acid. Compound appears to act by blocking the first step of TTR amyloid fibril formation and by destabilizing the transition states associated with TTR amyloid fibril formation, e.g., tetramer dissociation to the monomeric amyloidogenic intermediate. Potentially useful for the treatment of senile systemic amyloidosis and familial amyloid polyneuropathy. Another related *N*-phenyl phenoxazine inhibitor is:



285724: C₂₃ H₁₉ N O₅

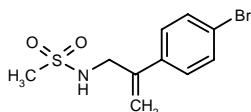
SOURCES – Scripps Research Institute, La Jolla, CA (US); Texas A&M University, College Station, TX (US).

REFERENCES

1. Petrassi, H.M. et al. *Structure-based design of N-phenyl phenoxazine transthyretin amyloid fibril inhibitors*. J Am Chem Soc 2000, 122(10): 2178.

285901

N-[2-(4-Bromophenyl)prop-2-enyl]methanesulfonamide



C₁₀ H₁₂ Br N O₂ S; Mol wt: 290.1798

ACTION – Glutamate receptor function modulator that acts by potentiating agonist-induced excitability of human GluR4B receptors and is thus expected to exhibit ampakine-like behavior *in vivo*. Claimed for the treatment of cognitive disorders, neurodegenerative disorders, age-related dementia and memory impairment, movement disorders, depression, attention deficit disorder, attention deficit hyperactivity disorder, psychosis, cognitive deficits associated with psychosis and drug-induced psychosis. A representative compound from a series of alkenyl sulfonamide derivatives.

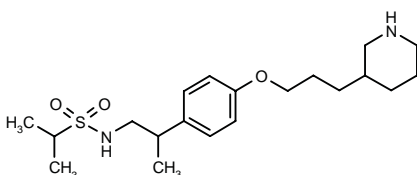
SOURCE – Lilly.

REFERENCES

1. Jones, W.D. et al. (Eli Lilly and Company) *Alkenyl sulphonamide derivs*. WO 0006539.

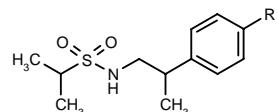
285916

N-[2-[4-[3-(3-Piperidinyl)propoxy]phenyl]propyl]propane-2-sulfonamide



C₂₀ H₃₄ N₂ O₃ S; Mol wt: 382.5656

ACTION – Agent for the treatment of cognitive disorders, neurodegenerative disorders, age-related dementia and memory impairment, movement disorders, depression, attention deficit disorder, attention deficit hyperactivity disorder, psychosis, cognitive deficits associated with psychosis and drug-induced psychosis that acts by potentiating agonist-induced excitability of human GluR4B receptors and is expected to exhibit ampakine-like behavior *in vivo*. Other exemplified compounds from this series of heterocyclyl sulfonamide derivatives include the following:



Compound	R1	Formula
285917	3-Pip-CH ₂ CH ₂ O	C ₁₉ H ₃₂ N ₂ O ₃ S
285918	4-Pip-(CH ₂) ₃ O	C ₂₀ H ₃₄ N ₂ O ₃ S
285919	1-Me-3-Pip	C ₁₈ H ₃₀ N ₂ O ₂ S
285920	1-Me-4-Pip	C ₁₈ H ₃₀ N ₂ O ₂ S

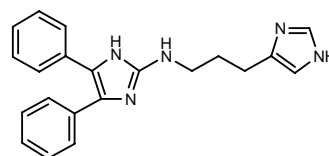
SOURCE – Lilly.

REFERENCES

1. Cantrell, B.E. et al. (Eli Lilly and Company) *Heterocyclyl sulphonamide derivs*. WO 0006158.

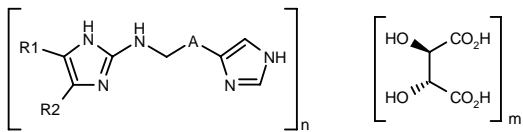
285922

N-(4,5-Diphenyl-1*H*-imidazol-2-yl)-*N*-[3-(1*H*-imidazol-4-yl)propyl]amine



C₂₁ H₂₁ N₅; Mol wt: 343.4319

ACTION – Histamine H₃ receptor ligand with IC₅₀ values in the range of 10-100 nM in a binding assay using [³H]-*N*^α-methylhistamine as the radioligand and rat brain homogenates. Potentially useful for the treatment or prevention of disorders linked to central and/or peripheral histaminergic system dysfunction such as age-related memory disturbances, Alzheimer's disease, Parkinson's disease, schizophrenia, depression, anxiety, sexual dysfunction, sleep disorders, migraine, epilepsy, hypertension, as well as inflammatory disorders, asthma, allergy, obesity, gastrointestinal disorders, metabolic disorders and pain. Other compounds within this series of 4-phenyl- and 4,5-diphenylimidazole derivatives include the following:



Compound	R1	R2	A	n	m	Formula
285923	H	4-F-Ph	-(CH2)2-	1	2	C ₁₅ H ₁₆ FN ₅ .2C ₄ H ₆ O ₆
285924	H	Ph	-(CH2)2-	2	3	2C ₁₅ H ₁₇ N ₅ .3C ₄ H ₆ O ₆
285925	H	4-MeO-Ph	-(CH2)2-	2	3	2C ₁₆ H ₁₉ N ₅ O.3C ₄ H ₆ O ₆
285927	H	4-Cl-3-Me-Ph	-(CH2)2-	2	1	C ₁₆ H ₁₈ ClN ₅ .2C ₄ H ₆ O ₆
285928	Ph	Me	-CH2-	2	5	2C ₁₅ H ₁₇ N ₅ .5C ₄ H ₆ O ₆
285929	H	Ph	-CH2-	2	1	C ₁₄ H ₁₅ N ₅ .2C ₄ H ₆ O ₆
285930	H	Ph	-(CH2)3-	2	1	C ₁₆ H ₁₉ N ₅ .2C ₄ H ₆ O ₆

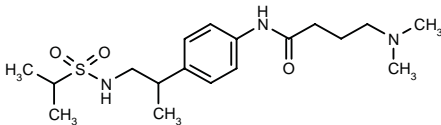
SOURCE – Sanofi-Synthélabo.

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1. Jegham, S. et al. (Sanofi-Synthélabo) 4-Phenyl- and 4,5-diphenylimidazole derivs., preparation and therapeutic application. FR 2781798, WO 0006552.

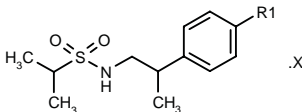
285972

4-(Dimethylamino)-N-[4-[2-(isopropylsulfonamido)-1-methylethyl]phenyl]butyramide



C18 H31 N3 O3 S; Mol wt: 369.5269

ACTION – Agent for the treatment of cognitive disorders, neurodegenerative disorders, age-related dementia and memory impairment, movement disorders, depression, attention deficit disorder, attention deficit hyperactivity disorder, psychosis, cognitive deficits associated with psychosis and drug-induced psychosis that acts by potentiating agonist-induced excitability of human GluR4B receptors and is expected to exhibit ampakine-like behavior *in vivo*. Other exemplified compounds from this series of sulfonamide derivatives include the following:



Compound	R1	X	Formula
285973	NHCO(CH2)3NHAc		C ₁₈ H ₂₉ N ₃ O ₄ S
285974	NHCOCH2OEt		C ₁₆ H ₂₆ N ₂ O ₄ S
285975	4-N(Me)2-1-Pip-CH2CONH		C ₂₁ H ₃₆ N ₄ O ₃ S
285978	1-Pip-CH2CH2O		C ₁₉ H ₃₂ N ₂ O ₃ S
285979	OCH2CH2OPh		C ₂₀ H ₂₇ NO ₄ S
285980	3-CF3-PhOCH2CH2O		C ₂₁ H ₂₆ F ₃ NO ₄ S
285981	OCH2CH2SPh		C ₂₀ H ₂₇ NO ₃ S ₂
285982	4-(AcOCH2CH2O)-Ph		C ₂₂ H ₂₉ NO ₅ S
285983	4-(4-morpholinyl-CH2CH2O)-Ph	HCl	C ₂₄ H ₃₄ N ₂ O ₄ S.HCl
285984	2-Pyr-OCH2CONH		C ₁₉ H ₂₅ N ₃ O ₄ S

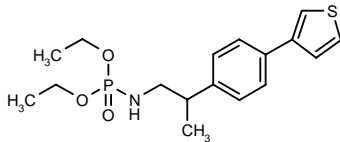
SOURCE – Lilly.

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1. Arnold, M.B. et al. (Eli Lilly and Company) Sulphonamide derivs. WO 0006148.

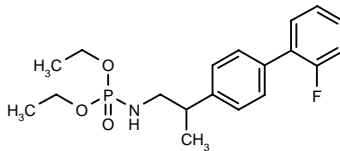
286141

N-[2-[4-(Thien-3-yl)phenyl]propyl]phosphoramidic acid diethyl ester



C17 H24 N O3 P S; Mol wt: 353.4206

ACTION – Agent for the treatment of cognitive disorders, neurodegenerative disorders, age-related dementia or memory impairment, movement disorders, depression, attention deficit disorder, attention deficit hyperactivity disorder, psychosis, cognitive deficits associated with psychosis and drug-induced psychosis that acts by potentiating agonist-induced excitability of the human GluR4B receptor and is thus expected to exhibit ampakine-like properties *in vivo*. Another specifically claimed compound from this series of amidophosphate derivatives is:



286142: C19 H25 F N O3 P

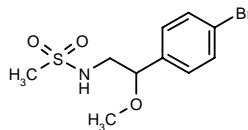
SOURCE – Lilly.

REFERENCES

1. Arnold, M.B. et al. (Eli Lilly and Company) Amidophosphate derivs. WO 0006176.

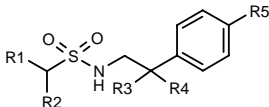
286157

N-[2-(4-Bromophenyl)-2-methoxyethyl]methanesulfonyl amide



C10 H14 Br N O3 S; Mol wt: 308.1946

ACTION – Agent for the treatment of cognitive disorders, neurodegenerative disorders, age-related dementia and memory impairment, movement disorders, depression, attention deficit disorder and attention deficit hyperactivity disorder, psychosis, cognitive deficits associated with psychosis and drug-induced psychosis that acts by potentiating agonist-induced excitability of the human GluR4B receptor and is therefore expected to exhibit ampakine-like behavior *in vivo*. Other exemplified compounds from this series of sulfonamide derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
286158	Me	Me	H	CF3	4-MeO-Ph	C ₁₉ H ₂₂ F ₃ NO ₃ S
286159	Me	Me	H	CF3	4-OH-Ph	C ₁₈ H ₂₀ F ₃ NO ₃ S
286160	H	H	H	OMe	3-thienyl	C ₁₄ H ₁₇ NO ₃ S ₂
286161	Me	Me	-CH2-		Ph	C ₁₈ H ₂₁ NO ₂ S
286162	Me	Me	F	F	Ph	C ₁₇ H ₁₉ F ₂ NO ₂ S
286163	Me	Me	H	F	Ph	C ₁₇ H ₂₀ FNO ₂ S

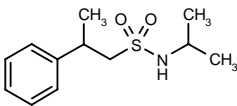
SOURCE – Lilly.

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1. Arnold, M.B. et al. (Eli Lilly and Company) *Sulphonamide derivs.* EP 0980864, WO 0006157.

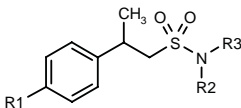
286179

N-(Isopropyl)-2-phenylpropanesulfonamide



C12 H19 N O2 S; Mol wt: 241.3531

ACTION – Agent for the treatment of cognitive disorders, neurodegenerative disorders, age-related dementia or memory impairment, movement disorders, depression, attention deficit disorder, attention deficit hyperactivity disorder, psychosis, cognitive deficits associated with psychosis and drug-induced psychosis that acts by potentiating agonist-induced excitability of the human GluR4B receptor and is thus expected to exhibit ampakine-like properties *in vivo*. Other specifically claimed compounds from this series of sulfonamide derivatives include the following:



Compound	R1	R2	R3	Formula
286180	Br	H	H	C ₉ H ₁₂ BrNO ₂ S
286181	2-F-Ph	H	Me	C ₁₆ H ₁₆ FNO ₂ S
286182	2-F-Ph	H	Et	C ₁₇ H ₂₀ FNO ₂ S
286183	2-F-Ph	H	i-Pr	C ₁₈ H ₂₂ FNO ₂ S
286184	2-F-Ph	Me	Me	C ₁₇ H ₂₀ FNO ₂ S
286185	2-F-Ph	H	(CH2)3N(Me)2	C ₂₀ H ₂₇ FN ₂ O ₂ S
286186	2-F-Ph	H	t-Bu	C ₁₉ H ₂₄ FNO ₂ S

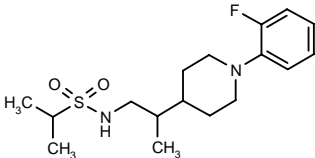
SOURCE – Lilly.

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1. Arnold, M.B. et al. (Eli Lilly and Company) *Sulfonamide derivs.* WO 0006149.

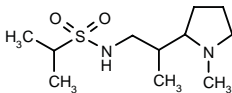
286189

N-[2-[1-(2-Fluorophenyl)piperidin-4-yl]propyl]propane-2-sulfonamide



C17 H27 F N2 O2 S; Mol wt: 342.4763

ACTION – Agent for the treatment of cognitive disorders, neurodegenerative disorders, age-related dementia and memory impairment, movement disorders, depression, attention deficit disorder and attention deficit hyperactivity disorder, psychosis, cognitive deficits associated with psychosis and drug-induced psychosis that acts by potentiating agonist-induced excitability of the human GluR4B receptor and is therefore expected to exhibit ampakine-like behavior *in vivo*. Another compound from this series of heterocyclic sulfonamides is:



286190: C11 H24 N2 O2 S

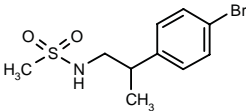
SOURCE – Lilly.

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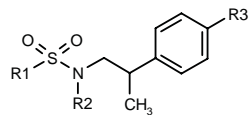
286313

N-[2-(4-Bromophenyl)propyl]methanesulfonamide



C10 H14 Br N O2 S; Mol wt: 292.1956

ACTION – Agent for the treatment of cognitive disorders, neurodegenerative disorders, age-related dementia and memory impairment, movement disorders, depression, attention deficit disorder and attention deficit hyperactivity disorder, psychosis, cognitive deficits associated with psychosis and drug-induced psychosis that is reported to potentiate agonist-induced excitability of the human GluR4B receptor and is therefore expected to exhibit ampakine-like behavior *in vivo*. Other compounds from this series of *N*-substituted sulfonamides include the following:



Compound	R1	R2	R3	Formula
286314	i-Pr	H	4-(NH2CH2CH2)-Ph	C20H28N2O2S
286315	Me	H	2-CHO-Ph	C17H19NO3S
286317	4-F-Ph	H	2-F-Ph	C21H19F2NO2S
286319	i-Pr	H	NHCOCH2Ph	C20H26N2O3S
286321	i-Pr	H	CH2CH(OH)Ph	C20H27NO3S
286322	i-Pr	Me	3-thienyl	C17H23NO2S2

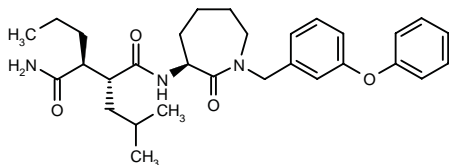
SOURCE – Lilly.

REFERENCES

1. Arnold, M.B. et al. (Eli Lilly and Company) *N*-Substd. sulfonamide derivs. WO 0006537.

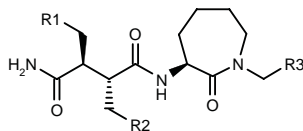
286447

2(R)-Isobutyl-N¹-[2-oxo-1-[3-(phenoxy)benzyl]-perhydroazepin-3(S)-yl]-3(S)-propylbutanediamide

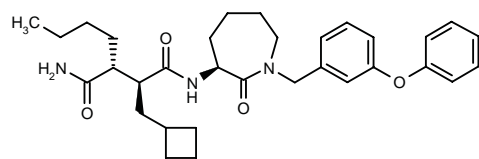


C30 H41 N3 O4; Mol wt: 507.6709

ACTION – Agent for the treatment of neurological disorders related to β-amyloid production such as Alzheimer’s disease and Down’s syndrome that inhibits the processing of amyloid precursor protein and, more specifically, the production of Aβ-peptide, thereby acting to prevent the formation of neurological amyloid protein deposits. Compound is believed to act by inhibiting γ-secretase activity. Other specifically claimed compounds from this series of succinoylamino lactams include the following:



Compound	R1	R2	R3	Formula
286449	Et	i-Pr	5-(4-CF3-Ph)-3-Pyr	C30H39F3N4O3
286452	vinyl	i-Pr	3-(2-Naph)-Ph	C34H41N3O3
286453	Et	cyclopropyl	3-[2,4-(Cl)2-Ph]-Ph	C30H37Cl2N3O3
286454	Pr	cyclopropyl	3-(PhO)-Ph	C31H41N3O4
286455	Et	cyclobutyl	3-[2,4-(Cl)2-Ph]-Ph	C31H39Cl2N3O3
286456	Pr	cyclobutyl	3-(PhO)-Ph	C32H43N3O4
286457	Et	cyclopentyl	3-[2,4-(Cl)2-Ph]-Ph	C32H41Cl2N3O3
286458	vinyl	i-Pr	cyclopentyl-CH2	C24H41N3O3



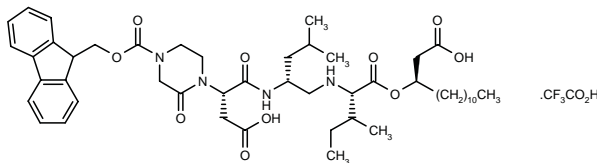
SOURCE – DuPont Pharmaceuticals.

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1. Olson, R.E. et al. (DuPont Pharmaceuticals Co.) *Succinoylamino lactams as inhibitors of Aβ protein production*. WO 0007995.

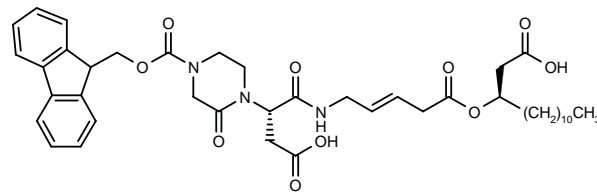
286599

3(R)-[2(S)-[2(R)-[3-Carboxy-2(S)-[4-(9H-fluoren-9-ylmethoxycarbonyl)-2-oxopiperazin-1-yl]propionamido]-4-methylpentylamino]-3-methylpentanoyloxy]tetradecanoic acid trifluoroacetate

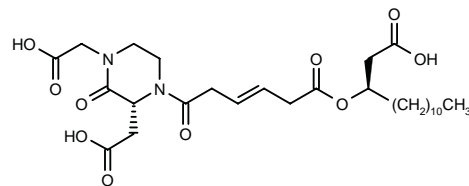


C49 H72 N4 O10 . C2 H F3 O2; Mol wt: 991.1477

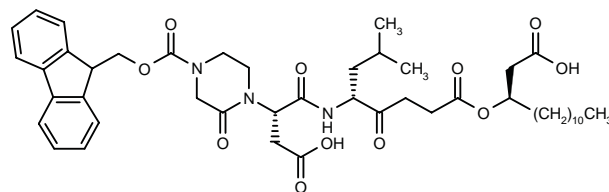
ACTION – Agent for the treatment of dementia, nerve injury and hyperlipidemia that acts by promoting the production of apolipoprotein E, as shown in HepG2 cells (280 and 458% increase at 1 and 5 μM, respectively, relative to control = 100%). Other exemplified compounds from this series of depsipeptides include the following:



286600: C42 H55 N3 O10



286601: C28 H44 N2 O10



286605: C46 H63 N3 O11

SOURCE – Nisshin Flour Milling.

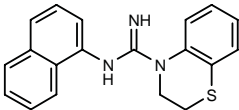
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1. Yanai, M. et al. (Nisshin Flour Milling Co., Ltd.) *Depsipeptide derivs. bearing piperazinone rings*. WO 0008047.

TREATMENT OF CEREBROVASCULAR DISEASES

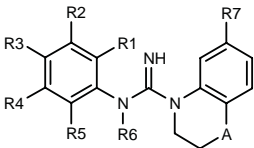
285874

N-(1-Naphthyl)-3,4-dihydro-2H-1,4-benzothiazine-4-carboxamide

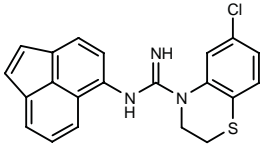


C19 H17 N3 S; Mol wt: 319.4303

ACTION – Neuroprotective agent for use in the treatment or prophylaxis of neurological injury and neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, cerebral palsy, epilepsy, stroke, heart attack, brain or spinal cord trauma, postsurgical neurological deficits and neurological deficits associated with cardiac arrest. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	A	Formula
285875	H	H	H	-CH=CH- CH=CH-	H	H	H	O	C ₁₉ H ₁₇ N ₃ O
285876	Br	H	H	Br	H	H	CF3	S	C ₁₆ H ₁₂ Br ₂ F ₃ N ₃ S
285877	F	H	H	CF3	H	H	Cl	S	C ₁₆ H ₁₂ ClF ₄ N ₃ S
285878	Br	H	H	Br	H	H	Cl	S	C ₁₅ H ₁₂ Br ₂ ClN ₃ S
285880	H	H	H	-CH=CH- CH=CH-	H	H	Cl	S	C ₁₉ H ₁₆ ClN ₃ S
285882	H	H	H	F	F	Me	H	S	C ₁₆ H ₁₅ F ₂ N ₃ S
285883	H	H	H	-CH=CH- CH=CH-	H	CF3	S	S	C ₂₀ H ₁₆ F ₃ N ₃ S
285884	H	H	H	-(CH2)4-	H	H	S	S	C ₁₉ H ₂₁ N ₃ S
285885	H	H	H	Ph	H	H	H	S	C ₂₁ H ₁₉ N ₃ S
285886	H	H	-CH=CH- CH=CH-	H	H	H	S	S	C ₁₉ H ₁₇ N ₃ S
285887	H	Cl	H	Cl	H	H	H	S	C ₁₅ H ₁₃ Cl ₂ N ₃ S
285888	H	H	H	F	F	H	H	S	C ₁₅ H ₁₃ F ₂ N ₃ S
285889	Br	H	H	Br	H	H	CF3	SO	C ₁₆ H ₁₂ Br ₂ F ₃ N ₃ OS
285890	Br	H	H	Br	H	H	CF3	SO2	C ₁₆ H ₁₂ Br ₂ F ₃ N ₃ O ₂ S
285891	-CH=CH- CH=CH-	H	H	H	H	CF3	SO	S	C ₂₀ H ₁₆ F ₃ N ₃ OS



285881: C21 H16 Cl N3 S

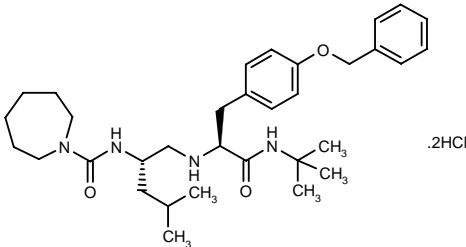
SOURCE – Cambridge NeuroScience.

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1. Reddy, N.L. et al. (Cambridge NeuroScience, Inc.) *Pharmaceutically active cpds. and methods of use*. US 6025355.

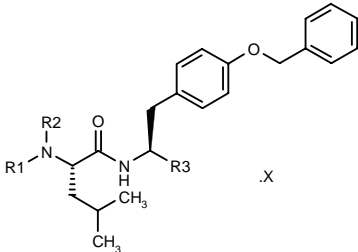
285931

4-O-Benzyl-N¹-(tert-butyl)-N²-[4-methyl-2(S)-(perhydroazepin-1-ylcarboxamido)pentyl]-L-tyrosinamide dihydrochloride

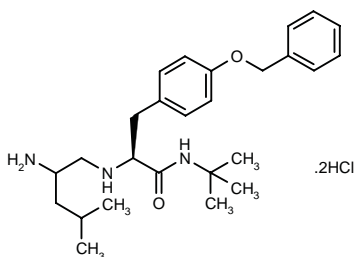


C33 H50 N4 O3 . 2HCl; Mol wt: 623.7048

ACTION – N-type calcium channel blocker proven to inhibit KCl-stimulated calcium flux into IMR-32 cells previously treated with nitrendipine to block L-type channels with an IC₅₀ value of 0.19 μM. Compound also provided 100% protection against audiogenic seizures in DBA/2 mice at 15 min posttreatment at a dose of 30 mg/kg i.v. Potentially useful for the treatment or prevention of stroke, cerebral ischemia, head trauma, epilepsy and pain. Other compounds within this series of reduced dipeptide derivatives include the following:



Compound	R1	R2	R3	X	Formula
285934	perhydro- -1-azepinyl-CO	H	CH2O-t-Bu		C ₃₃ H ₄₈ N ₃ O ₄
285935	Me	Me	4-morpholinyl- -CH2		C ₂₈ H ₄₁ N ₃ O ₃
285936	perhydro- -1-azepinyl-CO	H	4-morpholinyl- -CH2		C ₃₃ H ₄₈ N ₄ O ₄
285937	perhydro- -1-azepinyl-CO	H	t-BuNHCH2	CF3CO2H	C ₃₃ H ₅₀ N ₄ O ₃ .C ₂ HF ₃ O ₂
285938	perhydro- -1-azepinyl-CO	H	CH2N(Et)2		C ₃₃ H ₅₀ N ₄ O ₃



285939: C₂₆ H₃₉ N₃ O₂ . 2HCl

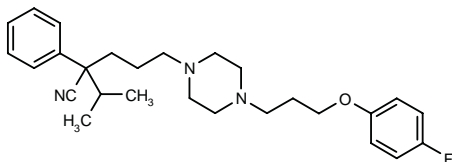
SOURCE – Warner-Lambert.

REFERENCES

1. Rafferty, M.F. and Song, Y. (Warner-Lambert Co.) *Reduced dipeptide analogues as calcium channel antagonists*. WO 0006559.

285985

5-[4-[3-(4-Fluorophenoxy)propyl]piperazin-1-yl]-2-iso-propyl-2-phenylpentanenitrile



C₂₇ H₃₆ F N₃ O; Mol wt: 437.5994

ACTION – Agent for the treatment of acute cerebrovascular disorders, stroke, head injury, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, pain, epilepsy, schizophrenia and other central and peripheral nervous system disorders, an inhibitor of voltage-dependent P/Q- or N-type calcium channels and of glutamate release. *In vitro*, compound gave IC₅₀ values of 5.9 μM in a Fura-2 assay for measuring intracellular Ca²⁺ levels in rat cerebral cortex synaptosomes and of 3.5 μM for inhibition of KCl-induced glutamate release from rat cerebral cortex slices. *In vivo*, compound was effective in reducing infarct volume in rat models of cerebral ischemia induced by middle cerebral artery occlusion with (40% reduction at 10 mg/kg i.v.) or without reperfusion (30% reduction at 20 mg/kg i.v.). In addition, compound exhibited analgesic activity in the formalin test in mice at 5-20 mg/kg i.v., being more potent than morphine.

SOURCE – Eisai.

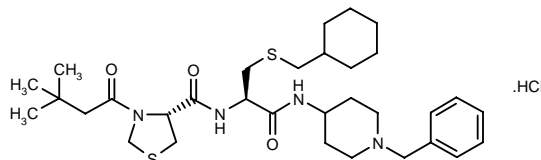
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285987

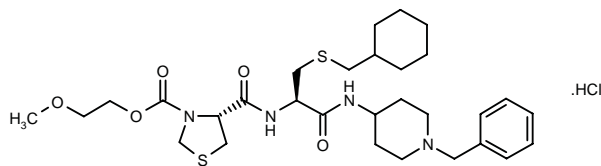
N-[1(*R*)-[*N*-(1-Benzylpiperidin-4-yl)carbamoyl]-2-(cyclohexylmethylsulfanyl)ethyl]-3-(3,3-dimethylbutyryl)-thiazolidine-4(*R*)-carboxamide hydrochloride

*N*¹-(1-Benzylpiperidin-4-yl)-*S*-(cyclohexylmethyl)-*N*²-[*N*-(3,3-dimethylbutyryl)-L-(4-thia)prolyl]-L-cysteinamide hydrochloride



C₃₂ H₅₀ N₄ O₃ S₂ . HCl; Mol wt: 639.3649

ACTION – N-type calcium channel antagonist shown to inhibit calcium influx in an *in vitro* assay and reported to have very low toxicity. Potentially useful in the treatment or prevention of cerebral infarction, transient cerebral ischemic attack, stress hypertension, epilepsy, asthma, frequent urination and pain. Another compound from this series of amino acid derivatives is:



285988: C₃₀ H₄₆ N₄ O₅ S₂ . HCl

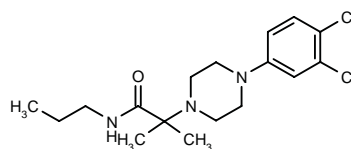
SOURCE – Ono.

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1. Seko, T. and Kato, M. (Ono Pharmaceutical Co., Ltd.) *Amino acid derivs. and drugs containing the same as the active ingredient*. WO 0004005.

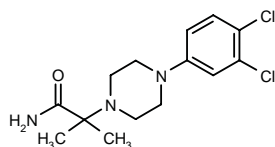
286491

2-[4-(3,4-Dichlorophenyl)piperazin-1-yl]-2-methyl-*N*-propylpropionamide

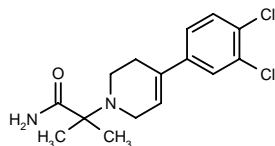


C₁₇ H₂₅ Cl₂ N₃ O; Mol wt: 358.3105

ACTION – Ionotropic glutamate receptor modulator with potential in the treatment of acute neurodegenerative diseases such as stroke, cerebral ischemia and head and spinal cord trauma, as well as chronic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, AIDS-induced dementia and Huntington's chorea. Compound may also be used as an antipsychotic, anticonvulsant, analgesic, antiemetic, anxiolytic and antidepressant agent. Other specifically claimed compounds include the following:



286492: C₁₄ H₁₉ Cl₂ N₃ O



286493: C₁₅ H₁₈ Cl₂ N₂ O

SOURCE – Lilly.

REFERENCES

1. Baker, S.R. et al. (Eli Lilly and Company) *Pharmaceutical cpsds*. WO 0008006.

AAVNMDAR1

286152

Adeno-associated virus (AAV) vaccine encoding mouse NMDAR1 cDNA which generates polyclonal autoantibodies against the NR1 subunit of the NMDA receptor (NMDAR1)

ACTION – Oral adeno-associated virus (AAV) vaccine which generates polyclonal autoantibodies against the NR1 subunit of the NMDA receptor (NMDAR1), proven to protect rat brain from stroke and to prevent kainate-induced seizures. The polyclonal autoantibodies generated by the vaccine were shown to bind only to receptors associated with epilepsy. After the oral administration of vaccine, transgene expression persisted for at least 5 months and was associated with a high humoral response in the absence of a significant cell-mediated response. Oral vaccination was shown to protect rats from kainate-induced epilepsy-like seizures (68 and 22% seizure frequency in controls and immunized rats, respectively) and to reduce infarct volume (70% reduction) and the resulting brain damage in an ET-1 model of middle cerebral artery occlusion in rats at 1 and 5 months following vaccination. Behavioral experiments in rats demonstrated that vaccination is not associated with impairment in motor behavior. NMDAR1 blockade is minimal under normal conditions where high serum antibody titers do not cross the blood–brain barrier, and increases under conditions of increased blood–brain barrier permeability resulting from neuronal insult. Potentially useful for the prevention of epilepsy and stroke.

SOURCES – University of Auckland, Auckland (NZ); Thomas Jefferson University, Philadelphia, PA (US).

REFERENCES

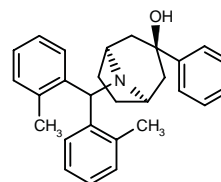
1. During, M.J. et al. *An oral vaccine against NMDAR1 with efficacy in experimental stroke and epilepsy*. *Science* 2000, 287(5457): 1453.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

286133

endo-8-[Bis(2-methylphenyl)methyl]-3-phenyl-8-aza-bicyclo[3.2.1]octan-3-ol



C₂₈ H₃₁ N O; Mol wt: 397.5589

ACTION – Agent for the treatment of pain, anxiety, cough, allergy or asthma symptoms, depression and alcohol abuse with high-affinity for the nociceptin ORL1 (N/OFQ) receptor. Agonist activity was demonstrated *in vivo* by stimulation of [³⁵S]-GTPγS binding to the human ORL1 receptor (101% at 100 nM). Antitussive activity was demonstrated in guinea pigs with capsaicin-induced cough at 1.0-10 mg/kg p.o.

SOURCE – Schering-Plough.

REFERENCES

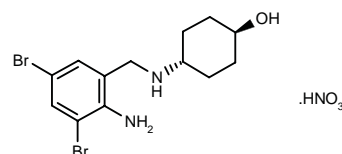
1. Tulshian, D. et al. (Schering Corp.) *High affinity ligands for nociceptin receptor ORL-1*. WO 0006545.

AMBROXOL NITRATE

Prop INNM

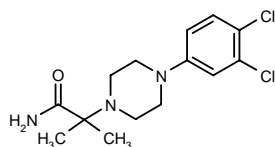
285902

trans-4-(2-Amino-3,5-dibromobenzylamino)cyclohexanol nitrate

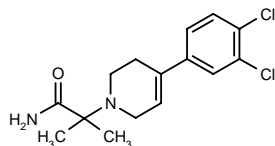


C₁₃ H₁₈ Br₂ N₂ O . H N O₃; Mol wt: 441.1181

ACTION – Nitrate salt of ambroxol shown to exhibit higher mucolytic activity than the corresponding hydrochloride in mice following i.p. administration. Another exemplified compound from this series of nitrate salts and nitrate esters of respiratory drugs expected to exhibit reduced side effects on the cardiovascular system and gastro-intestinal tract is:



286492: C₁₄ H₁₉ Cl₂ N₃ O



286493: C₁₅ H₁₈ Cl₂ N₂ O

SOURCE – Lilly.

REFERENCES

1. Baker, S.R. et al. (Eli Lilly and Company) *Pharmaceutical cpsds.* WO 0008006.

AAVNMDAR1

286152

Adeno-associated virus (AAV) vaccine encoding mouse NMDAR1 cDNA which generates polyclonal autoantibodies against the NR1 subunit of the NMDA receptor (NMDAR1)

ACTION – Oral adeno-associated virus (AAV) vaccine which generates polyclonal autoantibodies against the NR1 subunit of the NMDA receptor (NMDAR1), proven to protect rat brain from stroke and to prevent kainate-induced seizures. The polyclonal autoantibodies generated by the vaccine were shown to bind only to receptors associated with epilepsy. After the oral administration of vaccine, transgene expression persisted for at least 5 months and was associated with a high humoral response in the absence of a significant cell-mediated response. Oral vaccination was shown to protect rats from kainate-induced epilepsy-like seizures (68 and 22% seizure frequency in controls and immunized rats, respectively) and to reduce infarct volume (70% reduction) and the resulting brain damage in an ET-1 model of middle cerebral artery occlusion in rats at 1 and 5 months following vaccination. Behavioral experiments in rats demonstrated that vaccination is not associated with impairment in motor behavior. NMDAR1 blockade is minimal under normal conditions where high serum antibody titers do not cross the blood–brain barrier, and increases under conditions of increased blood–brain barrier permeability resulting from neuronal insult. Potentially useful for the prevention of epilepsy and stroke.

SOURCES – University of Auckland, Auckland (NZ); Thomas Jefferson University, Philadelphia, PA (US).

REFERENCES

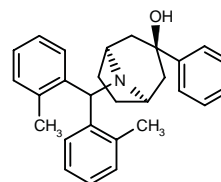
1. During, M.J. et al. *An oral vaccine against NMDAR1 with efficacy in experimental stroke and epilepsy.* Science 2000, 287(5457): 1453.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

286133

endo-8-[Bis(2-methylphenyl)methyl]-3-phenyl-8-aza-bicyclo[3.2.1]octan-3-ol



C₂₈ H₃₁ N O; Mol wt: 397.5589

ACTION – Agent for the treatment of pain, anxiety, cough, allergy or asthma symptoms, depression and alcohol abuse with high-affinity for the nociceptin ORL1 (N/OFQ) receptor. Agonist activity was demonstrated *in vivo* by stimulation of [³⁵S]-GTPγS binding to the human ORL1 receptor (101% at 100 nM). Antitussive activity was demonstrated in guinea pigs with capsaicin-induced cough at 1.0-10 mg/kg p.o.

SOURCE – Schering-Plough.

REFERENCES

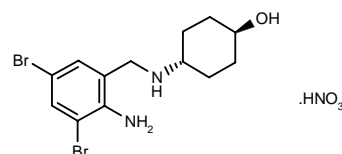
1. Tulshian, D. et al. (Schering Corp.) *High affinity ligands for nociceptin receptor ORL-1.* WO 0006545.

AMBROXOL NITRATE

Prop INNM

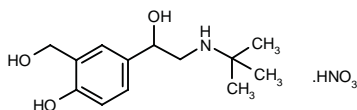
285902

trans-4-(2-Amino-3,5-dibromobenzylamino)cyclohexanol nitrate



C₁₃ H₁₈ Br₂ N₂ O . H N O₃; Mol wt: 441.1181

ACTION – Nitrate salt of ambroxol shown to exhibit higher mucolytic activity than the corresponding hydrochloride in mice following i.p. administration. Another exemplified compound from this series of nitrate salts and nitrate esters of respiratory drugs expected to exhibit reduced side effects on the cardiovascular system and gastro-intestinal tract is:



Salbutamol nitrate [285903]: C₁₃ H₂₁ N O₃ . H N O₃

SOURCE – NicOx.

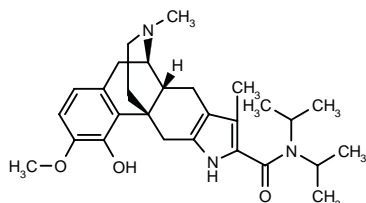
REFERENCES

1. Del Soldato, P. (NicOx SA) *Nitric esters and nitrate salts of specific drugs*. WO 0006531.

SB-227122

286268

4-Hydroxy-3-methoxy-4',17-dimethyl-6,7-didehydro-pyrrolo[2',3':6,7]morphinan-5'-carboxylic acid diisopropylamide



C₂₈ H₃₉ N₃ O₃; Mol wt: 465.6341

ACTION – Potent δ -opioid receptor agonist with nanomolar affinity for this receptor ($K_i = 6.9$ nM) and high selectivity over μ - and κ -opioid receptors ($K_i = 2030$ and > 5000 nM, respectively). In functional experiments, compound displayed full agonist activity, decreasing cAMP levels in CHO cells expressing human cloned δ -opioid receptors with an IC_{50} of 12 nM). *In vivo*, it exhibited antitussive activity in the guinea pig citric acid-induced cough model ($ED_{50} = 7.3$ mg/kg i.p.), an effect which was inhibited by the nonselective opioid receptor antagonist naloxone and by the δ -opioid receptor antagonist SB-244525, but not by the μ -, κ or σ -opioid receptor antagonists β -funaltrexamine, norbinaltorphimine and dextromethorphan, respectively. Potentially useful as an antitussive agent.

SOURCE – SmithKline Beecham.

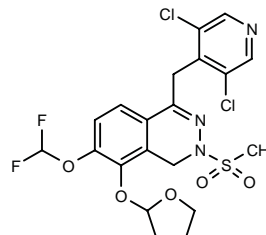
REFERENCES

1. Dondio, G. and Ronzoni, S. (SmithKline Beecham plc) *Heterocycle-condensed morphinoid derivs*. EP 0770081, JP 1998502657, US 5981540, WO 9602545.
2. Kotzer, C.J. et al. *The antitussive activity of delta-opioid receptor stimulation in guinea pigs*. J Pharmacol Exp Ther 2000, 292(2): 803.

ASTHMA THERAPY

285777

4-(3,5-Dichloropyridin-4-ylmethyl)-7-(difluoromethoxy)-2-(methylsulfonyl)-8-(tetrahydrofuran-2-yloxy)-1,2-dihydro-phthalazine



C₂₀ H₁₉ Cl₂ F₂ N₃ O₅ S; Mol wt: 522.3541

ACTION – Agent for the treatment of allergic and inflammatory disorders, particularly respiratory diseases, a potent inhibitor of phosphodiesterase type 4 (PDE4; $IC_{50} = 8 \pm 0.5$ nM).

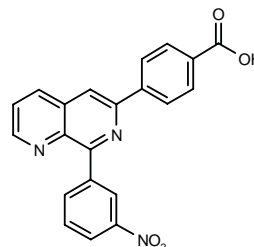
SOURCE – Zambon.

REFERENCES

1. Napoletano, M. et al. (Zambon Group SpA) *Phthalazine derivs. as phosphodiesterase 4 inhibitors*. WO 0005219.

285830

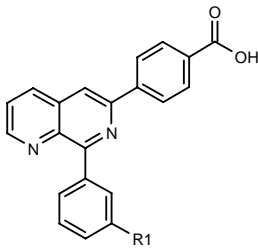
4-[8-(3-Nitrophenyl)-1,7-naphthyridin-6-yl]benzoic acid



C₂₁ H₁₃ N₃ O₄; Mol wt: 371.3507

M.p. > 250 °C.

ACTION – Phosphodiesterase type 4D (PDE4D) inhibitor ($IC_{50} = 1$ nM) that is 80-fold more potent than SB-207499 ($IC_{50} = 79$ nM) and has good selectivity against PDE4A, PDE4B and PDE4C ($IC_{50} = 88, 49$ and 68 nM, respectively). Compound was inactive against PDE3 although it was about 2-fold more potent in the rolipram binding assay ($IC_{50} = 0.6$ nM) than in the PDE4 enzyme assay. Compound strongly inhibited the fMLP-induced oxidative burst in human peripheral blood eosinophils ($IC_{50} = 0.7$ nM), indicating its ability to penetrate cells. In sensitized rats with antigen-induced pulmonary eosinophilia, compound (1 mg/kg p.o.) strongly inhibited eosinophil influx and eosinophil peroxidase production, and to a smaller extent, the infiltration of T-lymphocytes, neutrophils and the release of protein into bronchoalveolar lavage fluid. Potentially useful for the treatment of chronic inflammatory diseases such as asthma, chronic obstructive pulmonary disease and rheumatoid arthritis. Within this series of 1,7-naphthyridines, the following are also included:



Compound	R1	Formula
285831	Cl	C ₂₁ H ₁₃ ClN ₂ O ₂
285832	CN	C ₂₂ H ₁₃ N ₃ O ₂

SOURCE – Novartis.

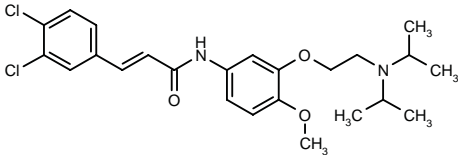
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1. Hersperger, R. (Novartis AG) *Naphtyridine derivs.* EP 0934320, WO 9818796.

2. Hersperger, R. et al. *Palladium-catalyzed cross-coupling reactions for the synthesis of 6,8-disubstituted 1,7-naphthyridines: A novel class of potent and selective phosphodiesterase type 4D inhibitors.* J Med Chem 2000, 43(4): 675.

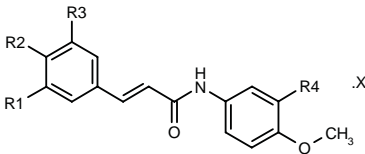
285964

3-(3,4-Dichlorophenyl)-N-[3-[2-(diisopropylamino)-ethoxy]-4-methoxyphenyl]-2-propenamide

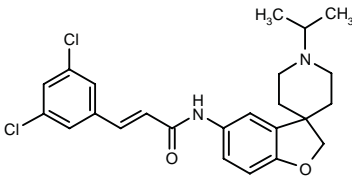


C24 H30 Cl2 N2 O3; Mol wt: 465.4180

ACTION – Chemokine CCR5 receptor modulator with potential in the treatment or prevention of disease states mediated by CCR5 such as chronic obstructive pulmonary disease, asthma, atopic disorders, rheumatoid arthritis, atherosclerosis, fibrotic disease, psoriasis, multiple sclerosis, inflammatory bowel disease and HIV infection. Other specifically claimed compounds from this series of substituted anilides include the following:



Compound	R1	R2	R3	R4	X	Formula
285965	-CH=CHCH=CH-		H	(CH2)3N(i-Pr)2	HCl	C ₂₈ H ₃₄ N ₂ O ₃ ·HCl
285966	H	Cl	Cl	2,2,6,6-(Me)4- -1-Pip-CH2CH2O		C ₂₇ H ₃₄ Cl ₂ N ₂ O ₃
285968	H	Cl	Cl	(CH2)3N(i-Pr)2		C ₂₈ H ₃₂ Cl ₂ N ₂ O ₂
285970	H	Cl	Cl	2,2,6,6-(Me)4-4-OH- -1-Pip-CH2CH2O		C ₂₇ H ₃₄ Cl ₂ N ₂ O ₄



285971: C24 H26 Cl2 N2 O2

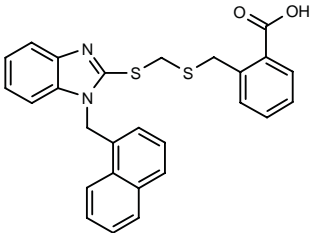
SOURCE – SmithKline Beecham.

REFERENCES

1. Bondinell, W.E. (SmithKline Beecham Corp.) *Propenamides as CCR5 modulators.* WO 0006153.

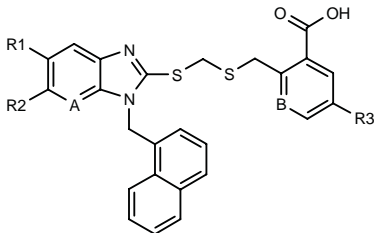
286051

2-[1-(1-Naphthylmethyl)-1H-benzimidazol-2-ylsulfanyl-methylsulfanylmethyl]benzoic acid



C27 H22 N2 O2 S2; Mol wt: 470.6148

ACTION – Human mast cell chymase inhibitor (IC₅₀ in the range 1-10 nM against activated human recombinant enzyme), with potential in the treatment of inflammatory, allergic, respiratory, cardiovascular and bone and cartilage disorders. A representative compound from a series of thiobenzimidazole derivatives, wherein the following are also included:



Compound	R1=R2	R3	A	B	Formula
286052	Me	H	CH	CH	C ₂₉ H ₂₆ N ₂ O ₂ S ₂
286053	Cl	H	CH	CH	C ₂₇ H ₂₀ Cl ₂ N ₂ O ₂ S ₂
286054	H	H	N	CH	C ₂₆ H ₂₁ N ₃ O ₂ S ₂
286055	Me	H	CH	N	C ₂₈ H ₂₅ N ₃ O ₂ S ₂
286056	Cl	Cl	CH	CH	C ₂₇ H ₁₉ Cl ₃ N ₂ O ₂ S ₂

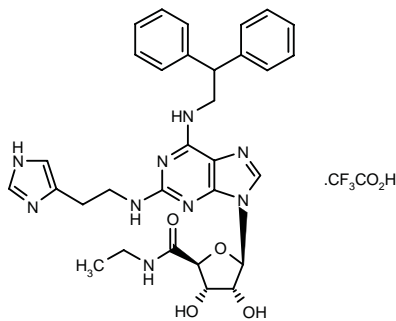
SOURCE – Teijin.

REFERENCES

1. Matsumoto, Y. et al. (Teijin Ltd.) *Thiobenzimidazole derivs.* WO 0003997.

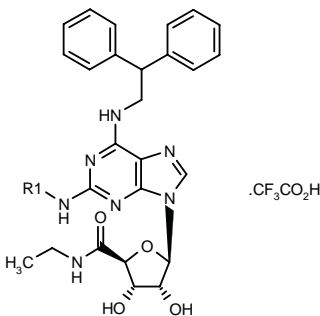
286096

1-Deoxy-[2-[2-(1*H*-imidazol-4-yl)ethylamino]-6-(2,2-diphenylethylamino)-9*H*-purin-9-yl]-*N*-ethyl-β-D-ribofuranuronamide trifluoroacetate



C31 H35 N9 O4 . C2 H F3 O2; Mol wt: 711.6984

ACTION – Adenosine A_{2A} receptor agonist with higher potency and selectivity relative to NECA (EC₅₀ compound/EC₅₀ NECA = 0.03 and 672 for A_{2A} and A₁ receptor agonism, respectively). Potentially useful for the treatment of inflammatory diseases. Other representative compounds within this series of adenosine analogues include the following:



Compound	R1	Isomer	Formula
286094	1-Pip-CH2CH2		C ₃₃ H ₄₂ N ₈ O ₄ ·C ₂ HF ₃ O ₂
286095	4-NH2-cyclohexyl	trans	C ₃₂ H ₄₀ N ₈ O ₄ ·C ₂ HF ₃ O ₂

SOURCE – Glaxo Wellcome.

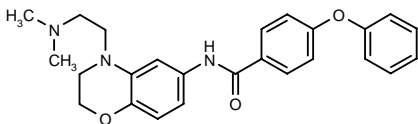
REFERENCES

1. Gregson, M. et al. (Glaxo Wellcome plc) *2,6-Diaminopurine derivs.* EP 0680488, JP 1996505864, US 5925624, WO 9417090.

2. Keeling, S.E. et al. *The discovery and synthesis of highly potent, A_{2A} receptor agonists.* Bioorg Med Chem Lett 2000, 10(4): 403.

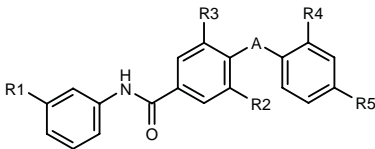
286251

N-[4-[2-(Dimethylamino)ethyl]-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl]-4-(phenoxy)benzamide

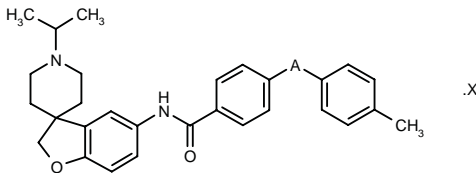


C25 H27 N3 O3; Mol wt: 417.5063

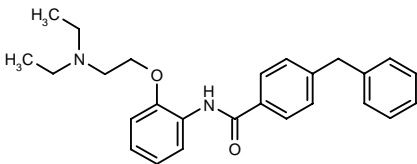
ACTION – Chemokine CCR5 receptor modulator with potential in the treatment of CCR5-mediated diseases such as chronic obstructive pulmonary disease (COPD), asthma and atopic diseases, rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic diseases, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease and HIV infection. Other specifically claimed compounds within this series of substituted anilide derivatives include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
286253	OCH2CH2-N(i-Pr)2	H	NO2	Cl	Cl	SO	C ₂₈ H ₃₁ Cl ₂ N ₃ O ₆ S
286254	2,2,6,6-(Me)4-1-Pip-CH2CH2O	H	H	H	H	-CO-	C ₃₂ H ₃₈ N ₂ O ₄
286255	OCH2CH2-N(i-Pr)2	NHBU	SO2-NH2	H	H	-O-	C ₃₂ H ₄₄ N ₄ O ₆ S
286256	(CH2)3-N(i-Pr)2	H	NO2	H	Me	SO2	C ₃₀ H ₃₇ N ₃ O ₇ S



Compound	A	X	Formula
286257	-CO-	CF3CO2H	C ₃₀ H ₃₂ N ₂ O ₃ ·C ₂ HF ₃ O ₂
286258	-S-		C ₂₉ H ₃₂ N ₂ O ₂ S



286252: C26 H30 N2 O2

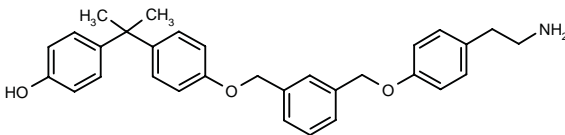
SOURCE – SmithKline Beecham.

REFERENCES

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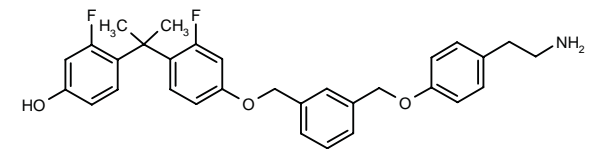
286349

4-[1-[4-[3-[4-(2-Aminoethyl)phenoxy)methyl]-benzyloxy]phenyl]-1-methylethyl]phenol



C31 H33 N O3; Mol wt: 467.6057

ACTION – Potent LTB₄ (BLT) receptor antagonist with potential in the treatment of asthma, chronic obstructive pulmonary disorder, chronic bronchitis, arthritis, psoriasis, ulcerative colitis, cystic fibrosis, Alzheimer’s disease, shock, ischemia–reperfusion injury, atherosclerosis and multiple sclerosis. Compound is reported to inhibit LTB₄-induced neutrophil accumulation in mouse ear with an ED₅₀ value in the range 0.02-0.03 mg/kg p.o. Another specifically claimed compound from this series of phenylethylamine derivatives is:



286350: C31 H31 F2 N O3

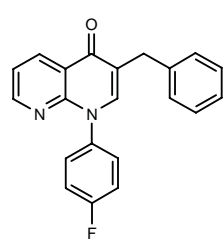
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Anderskewitz, R. et al. (Boehringer Ingelheim Pharma KG) *Novel phenylethylamine derivs., a method for the production thereof and their use as medicaments*. DE 19834713, WO 0007977.

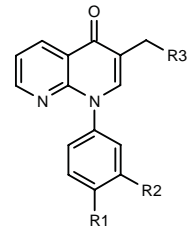
286505

3-Benzyl-1-(4-fluorophenyl)-1,8-naphthyridin-4(1*H*)-one



C21 H15 F N2 O; Mol wt: 330.3605

ACTION – A selective inhibitor of phosphodiesterase type 4 (PDE4), particularly the PDE4D isozyme, which plays a key role in regulating the activation and degranulation of human eosinophils, and of TNF production. Potentially useful in the treatment of asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, toxic shock, fibrosis, pulmonary hypersensitivity, allergic rhinitis, atopic dermatitis, psoriasis, rheumatoid arthritis, cachexia, Crohn’s disease, ulcerative colitis, arthritic conditions and other inflammatory disorders, depression, multiinfarct dementia and AIDS. Other exemplified compounds from this series of substituted 1,8-naphthyridin-4(1*H*)-ones include the following:



Compound	R1	R2	R3	Formula
286511	F	H	4-Ac-Ph	C ₂₃ H ₁₇ FN ₂ O ₂
286512	F	H	4-[MeCH(OH)]-Ph	C ₂₃ H ₁₉ FN ₂ O ₂
286513	H	N(Me)2	Ph	C ₂₃ H ₂₁ N ₃ O
286514	H	Cl	Ph	C ₂₁ H ₁₅ ClN ₂ O
286515	F	H	trans-4-[C(Me)2OH]-cyclohexyl	C ₂₈ H ₂₇ FN ₂ O ₂

SOURCE – Pfizer.

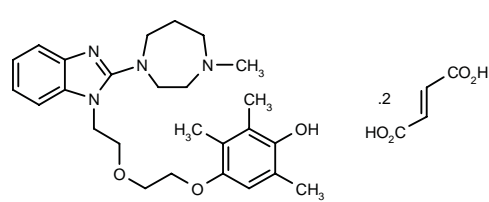
REFERENCES

1. Kleinman, E.F. (Pfizer Products Inc.) *Substd. 1,8-naphthyridin-4(1H)-ones as phosphodiesterase 4 inhibitors*. WO 0009504.

BOM-1006

283817

2,3,6-Trimethyl-4-[2-[2-[2-(4-methyl-1,4-perhydro-diazepin-1-yl)-1*H*-benzimidazol-1-yl]ethoxy]ethoxy]phenol difumarate



C26 H36 N4 O3 . 2 C4 H4 O4; Mol wt: 684.7386

ACTION – Antiallergic agent, an inhibitor of 5-lipoxygenase (IC₅₀ = 0.438 μM in RBL-1 cells) that strongly inhibits antigen-induced histamine release from sensitized rat peritoneal mast cells, prevents NADPH-dependent lipid peroxidation induced by Fe³⁺ and ADP in rat liver microsomes (IC₅₀ = 1.87 μM) and antagonizes histamine-induced contractions in guinea pig ileum (pA₂ = 7.49). *In vivo*, compound showed antiallergic activity, inhibiting the cutaneous PCA reaction in rat dorsal skin (3-30 mg/kg p.o.) with efficacy slightly weaker than that of emedastine. Potentially useful for the treatment of type I allergic diseases including bronchial asthma, allergic rhinitis, atopic dermatitis and pollenosis.

SOURCE – Fuji Yakuhin.

REFERENCES

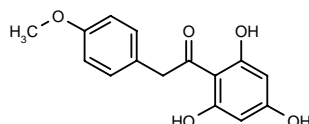
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D-58

286064

1-(2,4,6-Trihydroxyphenyl)-2-(4-methoxyphenyl)ethan-1-one



C15 H14 O5; Mol wt: 274.2706

ACTION – Antiallergic and antiinflammatory agent, an inhibitor of the tyrosine kinases SYK and BTK; it inhibits IgE receptor/FcεRI-mediated mast cell degranulation and LTC₄ release, as well as UVB-induced PGE₂ release from human keratinocytes. *In vivo*, compound was shown to prevent mast cell mediator-induced vascular permeability in a murine model of passive cutaneous anaphylaxis, inhibit the formation of skin edema in a UVB irradiation model in mice and inhibit PGE₂ and LTB₄ release and neutrophil influx in an air pouch model of inflammation. Potentially useful for the treatment of allergic and inflammatory disorders, including allergy, asthma, arthritis, psoriasis and sunburn.

SOURCE – Parker Hughes Institute, St. Paul, MN (US).

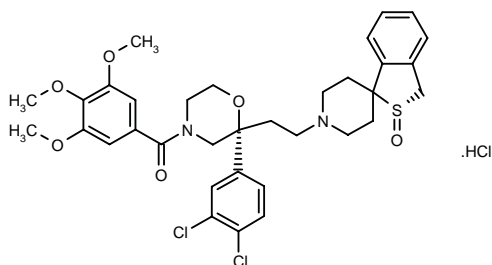
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R-113281*

272066

1'-[2-[2-(R)-(3,4-Dichlorophenyl)-4-(3,4,5-trimethoxybenzoyl)morpholin-2-yl]ethyl]spiro[benzo[c]thiophen-1(3H)-4'-piperidine] 2(S)-oxide hydrochloride



C34 H38 Cl2 N2 O6 S . HCl; Mol wt: 710.1151

ACTION – Selective tachykinin receptor antagonist with high affinity for NK₁, NK₂ and NK₃ receptor subtypes (K_i = 3.5, 1.9 and 1 nM, respectively, in guinea pig tissues); it also binds with nanomolar affinity to human NK₁, NK₂ and NK₃ receptors expressed in CHO cells and exhibits high selectivity over a number of other receptors. In guinea pigs, compound was shown to antagonize tracheal hyperpermeability induced by substance P, neurokinin B (NKB) and neurokinin A (NKA) at 0.1-0.33 mg/kg i.v., as well as the bronchoconstriction induced by NKA and NKB (ED₅₀ = 0.040-0.063 mg/kg i.v.). Potentially useful for the treatment of asthma, cough and bronchitis.

SOURCE – Sankyo.

REFERENCES

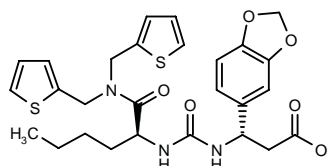
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*Identified compound **272066** Drug Data Rep 1999, 021(03): 0216.

TBC-3486*

281982

3(S)-(1,3-Benzodioxol-5-yl)-3-[N³-[1(S)-[N,N-bis(2-thienylmethyl)carbamoyl]pentyl]ureido]propionic acid



C27 H31 N3 O6 S2; Mol wt: 557.6889

ACTION – Antiinflammatory agent, a potent and selective VLA-4 antagonist (IC₅₀ = 0.4 nM for α₄β₁/CS-1 binding) with more than 100-fold selectivity over α₄β₇ receptors. *In vivo*, compound exhibited antiinflammatory activity in a lung inflammation model and the adjuvant arthritis model in rats (10 mg/kg s.c. b.i.d. for 22 days). Considered suitable for the treatment of asthma as an inhaled formulation.

SOURCE – Texas Biotechnology.

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*Identified compound **281982** Drug Data Rep 2000, 022(01): 0032.

AGENTS FOR RESPIRATORY
DISTRESS SYNDROME

CALFACTANT

USAN

217611

Calf lung surfactant extract obtained from the lavage of freshly killed calves that contains the essential phospholipids as well as surfactant-specific proteins SP-B and SP-C

An unmodified calf lung lavage extract containing mostly phospholipids and surfactant-specific proteins (SP-B and SP-C)

ACTION – Lung surfactant, an extract of natural surfactant from calf lungs with the ability to modify the alveolar surface tension similar to natural lung surfactant, thereby improving lung compliance, respiratory gas exchange and survival.

INDICATION – Prevention and treatment of respiratory distress syndrome in premature infants.

PROPRIETARY NAME – *Infasurf* (US).

PRESENTATION – Single-use vials (6 ml) containing a suspension for intratracheal instillation only, consisting of 35 mg/ml total phospholipids (including 26 mg phosphatidylcholine, of which 16 mg is disaturated phosphatidylcholine) and 0.65 mg/ml proteins (including 0.26 mg of SP-B, or surfactant-associated protein B).

SOURCES – Forest; licensed from Ony.

REFERENCES

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2. Bloom, B.T. et al. *Comparison of Infasurf (calf lung surfactant extract) to Survanta (beractant) in the treatment and prevention of respiratory distress syndrome*. Pediatrics 1997, 100(1): 31.

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27. *Forest Laboratories submits new drug application for Infasurf(R) to treat respiratory distress syndrome*. Forest Laboratories, Inc. Press Release 1995, March 4.

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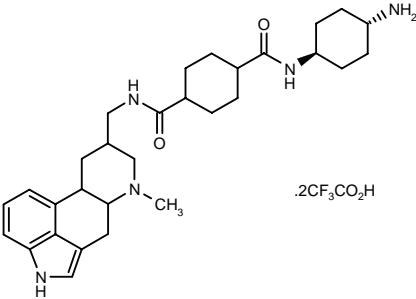
29. Forest Laboratories, Inc. First Quarter Report 1994, June 30.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

285388

*N*¹-(*trans*-4-Aminocyclohexyl)-*N*⁴-(7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-ylmethyl)-cyclohexane-1,4-dicarboxamide bis(trifluoroacetate)



C30 H43 N5 O2 . 2 C2 H F3 O2; Mol wt: 733.7465

AGENTS FOR RESPIRATORY
DISTRESS SYNDROME

CALFACTANT

USAN

217611

Calf lung surfactant extract obtained from the lavage of freshly killed calves that contains the essential phospholipids as well as surfactant-specific proteins SP-B and SP-C

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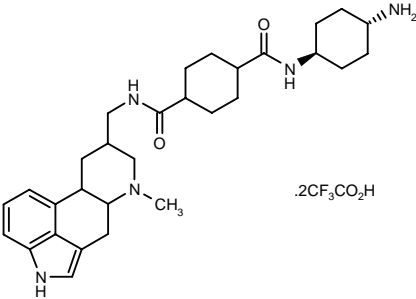
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

285388

*N*¹-(*trans*-4-Aminocyclohexyl)-*N*⁴-(7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-ylmethyl)-cyclohexane-1,4-dicarboxamide bis(trifluoroacetate)



C30 H43 N5 O2 . 2 C2 H F3 O2; Mol wt: 733.7465

ACTION – Antihypertensive agent, a representative compound from a series of ergoline derivatives proven to decrease blood pressure (> 30% decrease) in normotensive rats at 0.5 mg/kg i.v., with a duration of action of 60 min. Compound is believed to act by blocking α_1 -adrenoceptors.

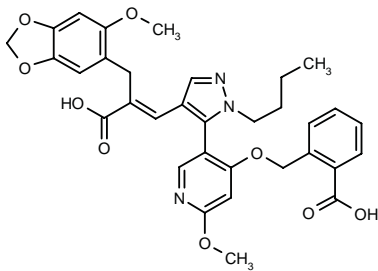
SOURCES – Hans Knöll Institute for Natural Product Research, Halle (DE); Friedrich-Schiller-Universität Jena, Jena (DE).

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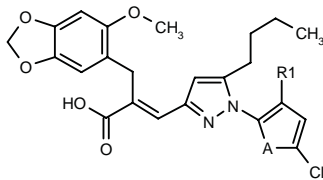
285653

2-[5-[1-Butyl-4-[2-carboxy-3-(6-methoxy-1,3-benzodioxol-5-yl)-1(E)-propenyl]-1H-pyrazol-5-yl]-2-methoxypyridin-4-yloxyethyl]benzoic acid

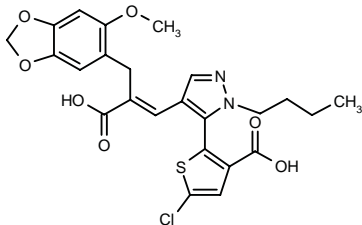


C33 H33 N3 O9; Mol wt: 615.6357

ACTION – Endothelin receptor antagonist with potential in the treatment of cardiovascular and renal diseases, particularly renal failure, hypertension, pulmonary hypertension and heart failure. Other specifically claimed compounds from this series of pyrazole derivatives include the following:



Compound	R1	A	Formula
285655	2-CO2H-PhCH2O	S	C ₃₁ H ₂₉ ClN ₂ O ₈ S
285656	CO2H	O	C ₂₄ H ₂₃ ClN ₂ O ₈



285654: C24 H23 Cl N2 O7 S

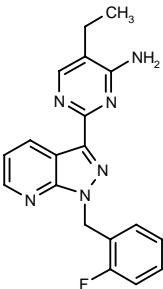
SOURCE – SmithKline Beecham.

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285801

5-Ethyl-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-amine



C19 H17 F N6; Mol wt: 348.3833

ACTION – Vasorelaxant and platelet aggregation inhibitor for the treatment of cardiovascular disorders such as hypertension, heart failure, angina pectoris and arrhythmias, thromboembolic disorders such as myocardial infarction and ischemia, restenosis following thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis and urogenital system disorders such as prostate hypertrophy, erectile dysfunction and urinary incontinence. *In vitro*, compound was found to potently stimulate guanylate cyclase in primary endothelial cells (> 1000% increase in cGMP levels at 1 μ M), to inhibit phenylephrine-induced contractions of guinea pig aorta strips (IC₅₀ = 280 nM) and to inhibit collagen-induced aggregation of human platelet-rich plasma (IC₅₀ = 6 nM). *In vivo*, it produced a maximum decrease in blood pressure of 11 and 24 mmHg when given to anesthetized rats at 1 and 3 mg/kg p.o., respectively.

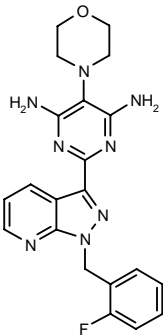
SOURCE – Bayer.

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1. Straub, A. et al. (Bayer AG) *3-(4-Amino-5-ethylpyrimidine-2-yl)-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine*. DE 19834045, WO 0006567.

285900

2-[1-(2-Fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-(4-morpholinyl)pyrimidine-4,6-diamine



C21 H21 F N8 O; Mol wt: 420.4499

ACTION – Vasorelaxant and platelet aggregation inhibitor for the treatment of cardiovascular disorders such as hypertension, heart failure, angina pectoris and arrhythmias, thromboembolic disorders such as myocardial infarction and ischemia, restenosis following thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis and urogenital system disorders such as prostatic hypertrophy, erectile dysfunction and urinary incontinence. *In vitro*, compound was found to stimulate guanylate cyclase in primary endothelial cells, as well as to inhibit phenylephrine-induced contractions of guinea pig aorta strips ($IC_{50} = 0.2 \mu M$) and to inhibit collagen-induced aggregation of human platelet-rich plasma ($IC_{50} = 0.06 \mu M$). *In vivo*, it produced a maximum decrease in blood pressure of 35 mmHg when given to anesthetized rats at 1.0 mg/kg p.o and was shown to dose-dependently decrease blood pressure in conscious spontaneously hypertensive rats at 0.3-10 mg/kg p.o.

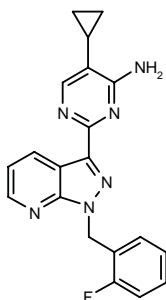
SOURCE – Bayer.

REFERENCES

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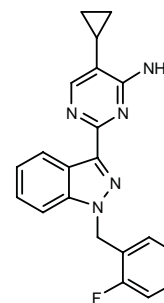
285913

5-Cyclopropyl-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-4-amine



C20 H17 F N6; Mol wt: 360.3943

ACTION – Vasorelaxant and platelet aggregation inhibitor for the treatment of cardiovascular disorders such as hypertension, heart failure, angina pectoris and arrhythmias, thromboembolic disorders such as myocardial infarction and ischemia, restenosis following thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis and urogenital system disorders such as prostatic hypertrophy, erectile dysfunction and urinary incontinence. *In vitro*, compound was found to stimulate guanylate cyclase in primary endothelial cells, as well as to inhibit phenylephrine-induced contractions of guinea pig aorta strips ($IC_{50} = 0.2 \mu M$) and to inhibit collagen-induced aggregation of human platelet-rich plasma ($IC_{50} = 0.003 \mu M$). *In vivo*, it produced a maximum decrease in blood pressure of 37 mmHg when given to anesthetized rats at 3 mg/kg p.o. In addition, compound was found to elicit penile erection in guinea pigs at 0.3-1 mg/kg i.v. and 30 mg/kg p.o., effects which were strongly potentiated by the coadministration of sodium nitroprusside. Another compound from this series of substituted pyrazole derivatives is:



285914: C21 H18 F N5

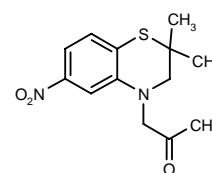
SOURCE – Bayer.

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286135

1-(2,2-Dimethyl-6-nitro-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)-2-propanone



C13 H16 N2 O3 S; Mol wt: 280.3464

ACTION – Potassium channel opener, a cromakalim derivative with about 20-fold more potent vasorelaxant activity than parent compound ($IC_{50} = 0.022$ and $0.39 \mu M$, respectively, for inhibition of 3,4-diaminopyridine-induced rhythmic contractions in dog coronary arteries). *In vivo* in anesthetized dogs, compound was able to decrease mean blood pressure (19% decrease at $10 \mu g/kg$ i.v.) with comparable potency to cromakalim. Potentially useful for the treatment of disorders caused by smooth muscle contraction such as hypertension, angina pectoris, asthma, urinary incontinence and baldness.

SOURCE – Yamanouchi.

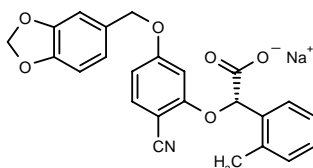
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1. Matsumoto, Y. et al. *Novel potassium channel openers. Part 4: Transformation of the 1,4-benzoxazine skeleton into 1,4-benzothiazine, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroquinoxaline, indoline, and 1,5-benzoxazepine*. Bioorg Med Chem 2000, 8(2): 393.

RPR-118031A

285390

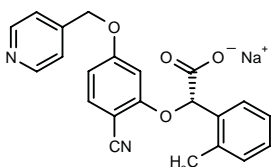
(+)-2(S)-[5-(1,3-Benzodioxol-5-ylmethoxy)-2-cyano-phenoxy]-2-(2-methylphenyl)acetic acid sodium salt



C24 H18 N Na O6; Mol wt: 439.3972

White solid, m.p. 212-4 °C.

ACTION – Potent and selective endothelin ET_A receptor antagonist with nanomolar affinity for this receptor (IC₅₀ = 6.7 nM), but no significant activity at ET_B receptors at up to 30 µM, and a pK_b of 8.1 for antagonizing ET-1-induced contractions in endothelium-denuded rat aorta. In pithed rats, compound was able to antagonize ET-1-induced increases in blood pressure after oral (75 µmol/kg) or i.v. (25 µmol/kg) administration. It showed a good pharmacokinetic profile in dogs, with a bioavailability of 89% and a half life of 7.4 h. Selected as a candidate for further development as a potential treatment for hypertension and pulmonary hypertension. Another phenoxyphenyl-acetic acid derivative with a similar *in vitro* profile but poor oral bioavailability is:



RPR-117820A [285391]: C22 H17 N2 Na O4

SOURCE – Aventis Pharma.

REFERENCES

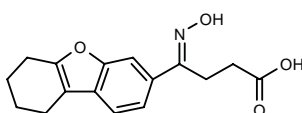
1. Porter, B. et al. (Rhône-Poulenc Rorer Ltd.) *Substd. phenyl cpds. as endothelin antagonists*. US 6048893, WO 9622978.

2. Astles, P.C. et al. *Selective ET_A antagonists. 5. Discovery and structure-activity relationships of phenoxyphenylacetic acid derivatives*. J Med Chem 2000, 43(5): 900.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

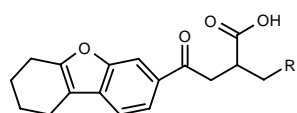
285905

4-(Hydroxyimino)-4-(6,7,8,9-tetrahydridibenzo[b,d]furan-3-yl)butyric acid



C16 H17 N O4; Mol wt: 287.3133

ACTION – An inhibitor of matrix metalloproteinases (MMPs), particularly gelatinase A (MMP-2), collagenase 3 (MMP-13), stromelysin 1 (MMP-3) and membrane-type MMP-1 (MMP-14), as demonstrated by IC₅₀ values against the catalytic domain of and full-length MMP-2 and the catalytic domains of MMP-3, MMP-13 and MMP-14 of 0.01835, 0.0595, 0.1145, 1.2067 and 0.24 µM, respectively, versus respective IC₅₀s of 100, 100 and 32 µM for full-length MMP-1, MMP-7 and MMP-9. Claimed for the treatment or prevention of atherosclerotic plaque rupture, aortic aneurysm, heart failure, restenosis, periodontal disease, corneal ulceration, burns, decubital ulcers, wounds, cancer, arthritis, osteoporosis, autoimmune or inflammatory disorders involving tissue invasion by leukocytes, multiple sclerosis, inflammation, pain, acute and chronic neurodegenerative disorders, renal disease and left ventricular dilatation. Other exemplified compounds from this series of tricyclic heteroaromatic derivatives include the following:



Compound	R1	Formula
285906	CH ₂ CH ₂ Ph	C ₂₅ H ₂₆ O ₄
285907	3,4,4-(Me)3-2,5-dioxo-1-imidazolidinyl	C ₂₃ H ₂₆ N ₂ O ₆

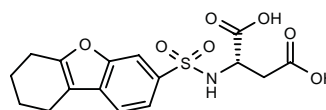
SOURCE – Warner-Lambert.

REFERENCES

1. O'Brien, P.M. et al. (Warner-Lambert Co.) *Tricyclic heteroaromatics and their derivs. as inhibitors of matrix metalloproteinases*. WO 0006560.

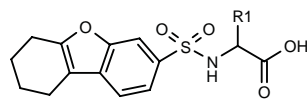
285909

2(S)-(6,7,8,9-Tetrahydridibenzo[b,d]furan-3-yl)sulfon-amido)succinic acid



C16 H17 N O7 S; Mol wt: 367.3763

ACTION – An inhibitor of matrix metalloproteinases (MMPs), particularly gelatinase A (MMP-2), collagenase 3 (MMP-13), stromelysin 1 (MMP-3) and membrane-type MMP-1 (MMP-14), as demonstrated *in vitro* by IC₅₀ values for the catalytic domain of and full-length MMP-2 and the catalytic domains of MMP-3, MMP-13 and MMP-14 of 0.0167, 0.45, 0.0056, 0.97 and 0.048 µM, respectively, versus IC₅₀ values of 16, 3.2 and 100 µM for full-length collagenase 1 (MMP-1), matrilysin (MMP-7) and gelatinase B (MMP-9). Claimed for the treatment and prevention of atherosclerotic plaque rupture, aortic aneurysm, heart failure, restenosis, periodontal disease, corneal ulceration, burns, decubital ulcers, wounds, cancer, arthritis, osteoporosis, autoimmune or inflammatory disorders involving tissue invasion by leukocytes, multiple sclerosis, inflammation and pain, acute and chronic neurodegenerative disorders, renal disease and left ventricular dilatation. Other compounds from this series of tricyclic sulfonamides include the following:



Compound	R1	Isomer	Formula
285910	i-Pr	R	C ₁₇ H ₂₁ NO ₅ S
285911	i-Pr	S	C ₁₇ H ₂₁ NO ₅ S
285912	CH ₂ CH ₂ Ph	S	C ₂₂ H ₂₃ NO ₅ S

SOURCE – Warner-Lambert.

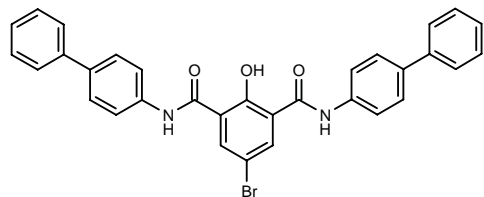
REFERENCES

1. O'Brien, P.M. et al. (Warner-Lambert Co.) *Tricyclic sulfonamides and their derivs. as inhibitors of matrix metalloproteinases*. WO 0006561.

285943

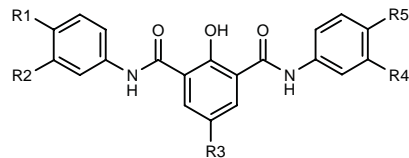
N¹,N³-Bis(4-biphenyl)-5-bromo-2-hydroxybenzene-1,3-dicarboxamide

N¹,N³-Bis(4-biphenyl)-5-bromo-2-hydroxyisophthalamide



C32 H23 Br N2 O3; Mol wt: 563.4487

ACTION – Macrophage scavenger receptor (MSR) antagonist useful for inhibiting lipid accumulation within macrophage-derived foam cells, expected to prevent plaque formation, retard plaque progression and initiate plaque regression via reversed cholesterol transport to acceptor HDL. Claimed for the treatment of cardiovascular disorders including atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia due to clotting, stroke, myocardial infarction, organ transplant, organ failure and hypercholesterolemia. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	R5	Formula
285944	Ph	H	CF ₃	H	Ph	C ₃₃ H ₂₃ F ₃ N ₂ O ₃
285945	Ph	H	H	H	Ph	C ₃₂ H ₂₄ N ₂ O ₃
285946	Cl	Cl	H	Cl	Cl	C ₂₀ H ₁₂ Cl ₄ N ₂ O ₃
285947	Cl	Cl	Br	Cl	Cl	C ₂₀ H ₁₁ BrCl ₄ N ₂ O ₃
285948	Cl	Cl	CF ₃	Cl	Cl	C ₂₁ H ₁₁ Cl ₄ F ₃ N ₂ O ₃
285950	Br	H	Br	H	Br	C ₂₀ H ₁₃ Br ₃ N ₂ O ₃
285951	Br	H	H	H	Br	C ₂₀ H ₁₄ Br ₂ N ₂ O ₃
285952	Br	H	CF ₃	H	Br	C ₂₁ H ₁₃ Br ₂ F ₃ N ₂ O ₃

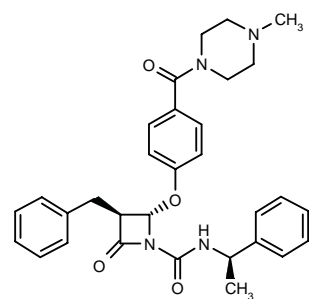
SOURCE – SmithKline Beecham.

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1. Franz, R.G. et al. (SmithKline Beecham Corp.) *Macrophage scavenger receptor antagonists*. WO 0006147.

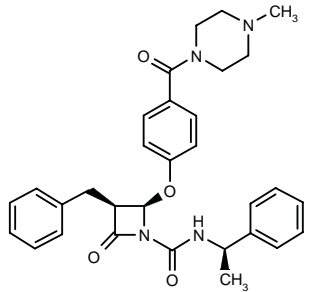
286062

3(S)-Benzyl-2(S)-[4-(4-methylpiperazin-1-ylcarbonyl)-phenoxy]-4-oxo-N-[1(R)-phenylethyl]azetidine-1-carboxamide



C31 H34 N4 O4; Mol wt: 526.6336

ACTION – Agent for the treatment or prevention of graft rejection, chronic inflammatory and fibrotic disorders such as heart failure or heart disease following myocardial infarction, cystic fibrosis, rheumatoid arthritis, asthma, atopic dermatitis, psoriasis, hepatitis, hepatic cirrhosis and inflammatory ocular diseases that acts by inhibiting human chymase (IC₅₀ = 0.46 nM) and the production of cytokines such as IL-1β, IL-2, IL-4, IL-5, IL-6, TNF-α and interferon gamma (IC₅₀ = 2.7, 2.7, 11.7, 6.5, 6.4, 1.9 and 12.1 μM, respectively, in concanavalin A-stimulated human blood mononuclear cells). Another compound from this series of monocyclic β-lactam derivatives is:



286063: C31 H34 N4 O4

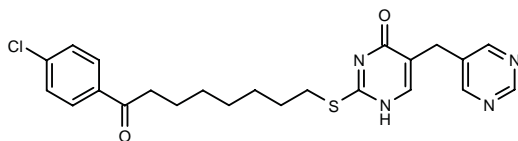
SOURCE – Shionogi.

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1. Uenaka, M. et al. (Shionogi & Co. Ltd.) *Monocyclic beta-lactam cpds. and chymase inhibitors containing the same*. WO 0005204.

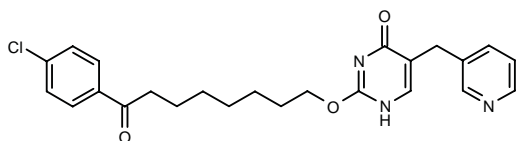
286091

2-[8-(4-Chlorophenyl)-8-oxooctylsulfanyl]-5-(5-pyrimidinylmethyl)pyrimidin-4(1*H*)-one



C23 H25 Cl N4 O2 S; Mol wt: 456.9955

ACTION – Potent, fully reversible and non-time-dependent inhibitor of lipoprotein-associated phospholipase A₂ (Lp-PLA₂; IC₅₀ = 54 nM) with high selectivity relative to the closely related human serine-dependent PLA₂. Potentially useful for the treatment of atherosclerosis or as a tool for evaluating the role of Lp-PLA₂ in this condition. Within this series of 2-(alkylthio)pyrimidin-4-ones, the following is also included:



286092: C24 H26 Cl N3 O3

SOURCE – SmithKline Beecham.

REFERENCES

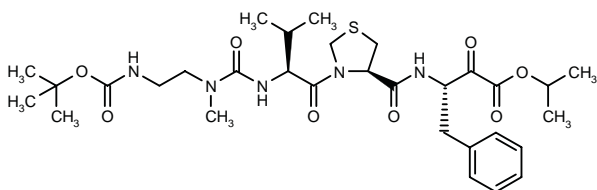
1. Hickey, D.M.B. et al. (SmithKline Beecham plc) *Pyrimidinone cpds. and pharmaceutical compns. containing them*. WO 9924420.

2. Boyd, H.F. et al. *2-(Alkylthio)pyrimidin-4-ones as novel, reversible inhibitors of lipoprotein-associated phospholipase A₂*. Bioorg Med Chem Lett 2000, 10(4): 395.

286118

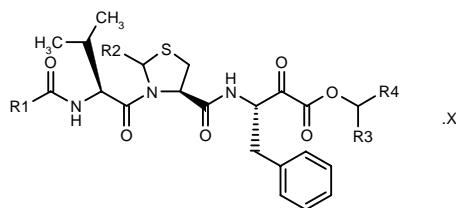
3(*S*)-[3-[2(*S*)-[3-[2-(*tert*-Butoxycarbonylamino)ethyl]-3-methylureido]-3-methylbutyryl]thiazolidin-4(*R*)-ylcarbox-amido]-2-oxo-4-phenylbutyric acid isopropyl ester

N-[*N*-[2-(*tert*-Butoxycarbonylamino)ethyl]-*N*-methyl-carbamoyl]-*L*-valyl-*L*-(4-thia)prolyl-*L*-phenylalanyl-carboxylic acid isopropyl ester



C31 H47 N5 O8 S; Mol wt: 649.8053

ACTION – Agent for the treatment of myocardial infarction, heart failure, restenosis following percutaneous transluminal coronary angioplasty (PTCA), hypertension, diabetic complications, allergic diseases and asthma with potent chymase-inhibitory activity (IC₅₀ = 12 nM against enzyme from canine left ventricle homogenates). Other compounds from this series of thiazolidine derivatives include the following:



Compound	R1	R2	R3	R4	X	Formula
286119	OCH2Ph	H	Me	Me		C ₃₀ H ₃₇ N ₃ O ₇ S
286120	CH2OMe	H	Me	Me		C ₂₅ H ₃₅ N ₃ O ₇ S
286121	CH2OPh	H	Me	Me		C ₃₀ H ₃₇ N ₃ O ₇ S
286123	<i>t</i> -BuO	H	Me	Me		C ₂₇ H ₃₉ N ₃ O ₇ S
286125	N(Me)CH2Ph	H	Me	Me		C ₃₁ H ₄₀ N ₄ O ₆ S
286126	OCH2Ph	H	Ph	H		C ₃₄ H ₃₇ N ₃ O ₇ S
286127	N(Me)CH2CH2NH2	Ph	Me	Me	HCl	C ₃₂ H ₄₃ N ₅ O ₆ S.HCl

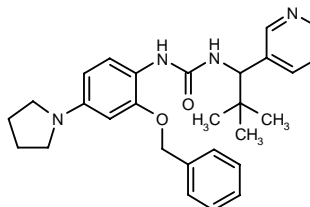
SOURCE – Santen.

REFERENCES

1. Nishimura, K. et al. (Santen Pharmaceutical Co., Ltd.) *Novel thiazolidine derivs.* JP 2000103785, WO 0006594.

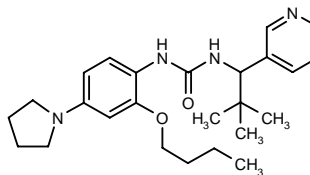
286197

N-[2-Benzoyloxy-4-(1-pyrrolidinyl)phenyl]-*N'*-[2,2-dimethyl-1-(3-pyridyl)propyl]urea



C28 H34 N4 O2; Mol wt: 458.6026

ACTION – Antiatherosclerotic agent, an ACAT inhibitor (IC₅₀ = 197 ng/ml against enzyme from rat hepatic microsomes) that also inhibits lipid peroxidation (IC₅₀ = 0.13 µg/ml in rat hepatic microsomes). Another compound from this series of phenylenediamine derivatives is:



286198: C25 H36 N4 O2

SOURCE – Sankyo.

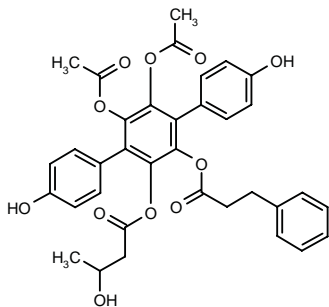
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1. Yanagisawa, H. et al. (Sankyo Co., Ltd.) *Phenylenediamine derivs.* JP 2000026293.

CURTISIAN D

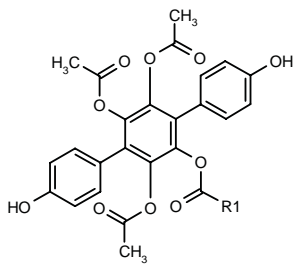
286004

2',3''-Bis(acetoxy)-5'-(3-hydroxybutyryloxy)-6'-(3-phenyl-propionyloxy)[1,1':4,1'']terphenyl-4,4''-diol



C35 H32 O11; Mol wt: 628.6268

ACTION – Free radical scavenger isolated from the methanolic extract of the fruit body of *Paxillus curtisii*, proven to inhibit lipid peroxidation induced by Fe(II)-ascorbic acid in rat liver microsomes (IC₅₀ = 0.14 µg/ml) and to scavenge superoxide radicals generated by the xanthine/xanthine oxidase system (IC₅₀ = 28.3 µg/ml). Compound did not exhibit DPPH radical-scavenging activity. In comparison with other free radical scavengers, compound was 20-fold more potent than vitamin E in inhibiting lipid peroxidation in rat liver microsomes and exhibited comparable activity to butylated hydroxyanisole in superoxide radical-scavenging activity. Potentially useful for the treatment of various diseases where free radicals are involved including myocardial and cerebral ischemia, atherosclerosis, diabetes, rheumatoid arthritis, cancer and the aging process. Other related compounds from this source are:



Compound	R1	Formula
Curtisian A [286001]	Ph	C ₃₁ H ₂₄ O ₁₀
Curtisian B [286002]	CH ₂ CH ₂ Ph	C ₃₃ H ₂₈ O ₁₀

SOURCE – Korea Research Institute of Bioscience and Biotechnology, Taedok Science Town (KR).

REFERENCES

1. Yun, B.-S. et al. *Curtisians A-D, new free radical scavengers from the mushroom Paxillus curtisii*. J Antibiot 2000, 53(2): 114.

USURPIN-α

285761

ACTION – Endogenous mammalian protein showing homology with procaspase 8 and procaspase 10, including tandem death effector domains (DEDs) on the N-terminus and a large-subunit/small-subunit caspase-like domain, but which lacks key residues that are necessary for caspase proteolytic activity. Compound is reported to heterodimerize with procaspase 8 and prevent procaspase 8 recruitment by the FADD/MORT1 adapter protein, thus blocking activation by the CD95 (Fas/APO-1) receptor complex, and may thus be used to modulate CD95(Fas/APO-1)-mediated apoptosis. It was shown to attenuate Jurkat T-lymphocyte cell death mediated by caspase 8 activation. Evidence was also presented indicating the involvement of the loss of usurpin and the simultaneous increase in the proapoptotic protease caspase 3 in the vulnerability of cardiac myocytes to apoptotic cell death following ischemia/reperfusion injury.

Usurpin-β [285762]

Usurpin-γ [285763]

SOURCE – Merck Frosst.

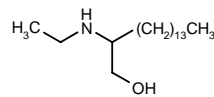
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1. Nicholson, D.W. et al. (Merck Frosst Canada Inc.) *Usurpin, a mammalian DED-caspase homologue that precludes caspase-8 recruitment and activation by the CD-95 (Fas, APO-1) receptor complex*. WO 0003023.

TREATMENT OF SHOCK

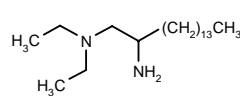
285767

2-(Ethylamino)-1-hexadecanol



C18 H39 N O; Mol wt: 285.5121

ACTION – Phospholipase A₂ (PLA₂) inhibitor with selectivity for secretory PLA₂ (IC₅₀ = 1.4, 3.7, 6.1 and 6.2 µM, respectively, against porcine pancreatic, recombinant human synovial, bee venom and *Naja naja* venom enzyme, respectively) relative to cytosolic PLA₂ (IC₅₀ > 200 µM). Potentially useful as an antiinflammatory agent for the treatment of septic shock, adult respiratory distress syndrome, arthritis and acute pancreatitis. Another related compound is:



285768: C20 H44 N2

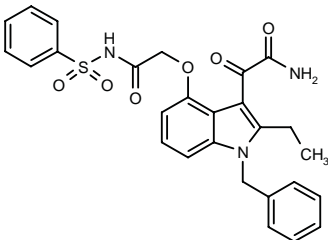
SOURCES – Universidad de Salamanca, Salamanca (ES); Universidad de Valencia, Valencia (ES).

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1. Lucas, R. et al. *Synthesis and enzyme inhibitory activities of a series of lipidic diamine and aminoalcohol derivatives on cytosolic and secretory phospholipases A₂*. Bioorg Med Chem Lett 2000, 10(3): 285.

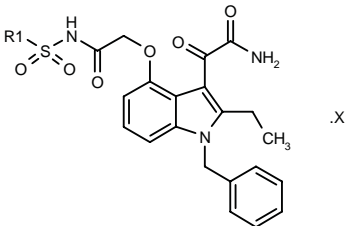
286335

2-[1-Benzyl-2-ethyl-4-[N-(phenylsulfonyl)carbamoylmethoxy]-1*H*-indol-3-yl]-2-oxoacetamide



C27 H25 N3 O6 S; Mol wt: 519.5755

ACTION – An inhibitor of human nonpancreatic secretory phospholipase A₂ (sPLA₂; IC₅₀ = 7 nM against human recombinant enzyme) with potential in the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis and inflammatory bowel disease. Other compounds from this series of acylsulfonamide substituted indole derivatives include the following:



Compound	R1	X	Formula
286336	Me		C ₂₂ H ₂₃ N ₃ O ₆ S
286337	CF ₃		C ₂₂ H ₂₀ F ₃ N ₃ O ₆ S
286338	2-Me-Ph		C ₂₈ H ₂₇ N ₃ O ₆ S
286339	4-(NH ₂ CH ₂ CH ₂)-Ph	HCl	C ₂₉ H ₃₀ N ₄ O ₆ S.HCl

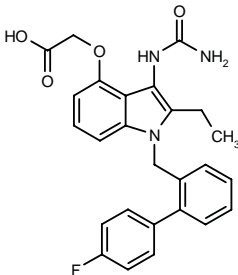
SOURCE – Lilly.

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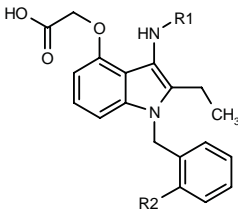
286427

2-[2-Ethyl-1-(4'-fluorobiphenyl-2-ylmethyl)-3-ureido-1*H*-indol-4-yloxy]acetic acid



C26 H24 F N3 O4; Mol wt: 461.4906

ACTION – Agent for the treatment of septic shock, inflammatory bowel disease, adult respiratory distress syndrome, pancreatitis, trauma, asthma, allergic rhinitis, rheumatoid arthritis and osteoarthritis, an inhibitor of human secretory phospholipase A₂ (sPLA₂; IC₅₀ = 0.017 μM against recombinant human enzyme). Other compounds within this series of indole derivatives include the following:



Compound	R1	R2	Formula
286428	CONH2	H	C ₂₀ H ₂₁ N ₃ O ₄
286432	Ac	H	C ₂₁ H ₂₂ N ₂ O ₄
286434	COCF ₃	H	C ₂₁ H ₁₉ F ₃ N ₂ O ₄
286438	COCH ₂ Br	H	C ₂₁ H ₂₁ BrN ₂ O ₄
286439	CSNH ₂	H	C ₂₀ H ₂₁ N ₃ O ₃ S
286440	COCONH ₂	H	C ₂₁ H ₂₁ N ₃ O ₅
286441	CONH ₂	Ph	C ₂₆ H ₂₅ N ₃ O ₄
286443	CONH ₂	Br	C ₂₀ H ₂₀ BrN ₃ O ₄

SOURCE – Lilly.

REFERENCES

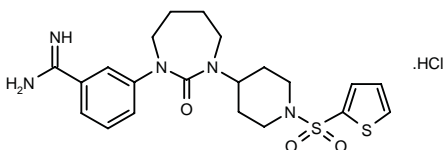
1. Bach, N.J. et al. (Eli Lilly and Company) *Indole sPLA₂ inhibitors*. WO 0007590.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

285848

3-[2-Oxo-3-[1-(2-thienylsulfonyl)piperidin-4-yl]perhydro-1,3-diazepin-1-yl]benzamidinium hydrochloride



C21 H27 N5 O3 S2 . HCl; Mol wt: 498.0692

ACTION – Anticoagulant, a factor Xa inhibitor ($K_i = 12$ nM) with high selectivity as regards thrombin ($K_i = 1500$ nM) but only 4-fold selectivity over trypsin ($K_i = 52$ nM). Compound was shown to inhibit thrombus formation in a rabbit arteriovenous shunt model of thrombosis with an ID_{50} of $7 \mu\text{mol/kg}$ i.v. It exhibited a good i.v. pharmacokinetic profile in rabbits with a half-life of 1 h and a C_{max} of $36 \mu\text{M}$ (after administration of 5 mg/kg), but measurement of Caco-2 monolayer permeation suggested poor oral absorption.

SOURCE – DuPont Pharmaceuticals.

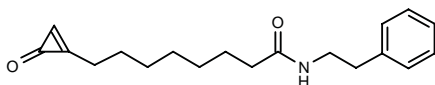
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2. Galembo, R.A. Jr. et al. *The de novo design and synthesis of cyclic urea inhibitors of factor Xa: Optimization of the S4 ligand*. Bioorg Med Chem Lett 2000, 10(3): 301.

285962

8-(3-Oxo-1-cyclopropen-1-yl)-*N*-(2-phenylethyl)octanamide



C19 H25 N O2; Mol wt: 299.4115

ACTION – Anticoagulant, an amide derivative of the fungal metabolite alutacenoic acid B, proven to strongly and irreversibly inhibit factor XIIIa ($IC_{50} = 26$ nM). Potentially useful for the treatment of thrombosis, atherosclerosis and coronary artery disease.

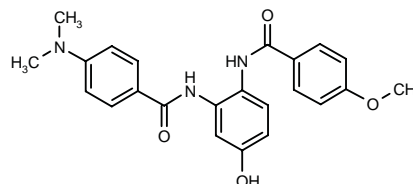
SOURCE – Sankyo.

REFERENCES

1. Kogen, H. et al. *Alutacenoic acids A and B, rare naturally occurring cyclopropenone derivatives isolated from fungi: Potent non-peptide factor XIIIa inhibitors*. J Am Chem Soc 2000, 122(8): 1842.

286320

N-[2-[4-(Dimethylamino)benzamido]-4-hydroxyphenyl]-4-methoxybenzamide



C23 H23 N3 O4; Mol wt: 405.4517

ACTION – Anticoagulant, an inhibitor of human factor Xa with high selectivity over human thrombin.

SOURCE – Lilly.

REFERENCES

1. Beight, D.W. et al. (Eli Lilly and Company) *Antithrombotic agents*. WO 9900121.

2. Herron, D.K. et al. *1,2-Dibenzamidobenzene inhibitors of human factor Xa*. J Med Chem 2000, 43(5): 859.

Hu-AJvW-2

286718

Humanized monoclonal antibody against human von Willebrand factor

ACTION – Antithrombotic agent, a humanized form of the murine anti-von Willebrand factor antibody AJvW-2 with comparable binding affinity.

SOURCE – Ajinomoto.

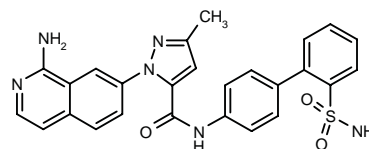
REFERENCES

1. Co, M.S. and Vasquez, M. (Ajinomoto Co., Inc.) *Antithrombotic agent and humanized-von Willebrand factor monoclonal antibody*. WO 0010601.

SQ-311

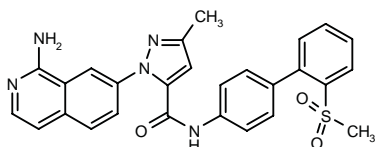
286969

1-(1-Aminoisoquinolin-7-yl)-*N*-(2'-sulfamoylbiphenyl-4-yl)-3-methyl-1*H*-pyrazole-5-carboxamide



C26 H22 N6 O3 S; Mol wt: 498.5648

ACTION – Oral anticoagulant, an inhibitor of factor Xa potentially useful for the treatment or prevention of thromboembolic disorders including unstable angina, myocardial infarction, transient ischemic attack, stroke, thrombosis and atherosclerosis. Another benzamidinium/guanidine mimetic is:



SQ-315 [286970]: C27 H23 N5 O3 S

SOURCE – DuPont Pharmaceuticals.

REFERENCES

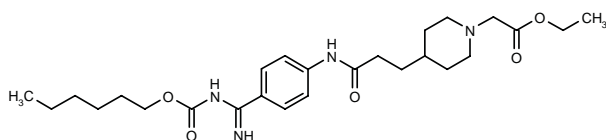
1. Lam, P.Y. et al. (DuPont Pharmaceuticals Co.) *Novel guanidine mimics as factor Xa inhibitors*. EP 0991638, WO 9857951.

2. Lam, P.Y.S. et al. *Structure-based design and discovery of orally bioavailable potent nonbenzamidine factor Xa inhibitors*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MED1 160.

ANTIPLATELET THERAPY

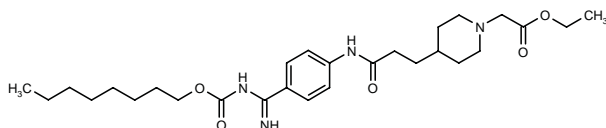
285775

2-[4-[2-[N-[4-(Hexyloxycarbonylamidino)phenyl]-carbamoyl]ethyl]piperidin-1-yl]acetic acid ethyl ester



C26 H40 N4 O5; Mol wt: 488.6250

ACTION – Antithrombotic agent, a specifically claimed compound from a series of substituted phenylamidines. Another specifically claimed compound is:



285776: C28 H44 N4 O5

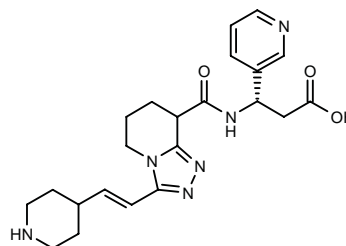
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Himmelsbach, F. et al. (Boehringer Ingelheim Pharma KG) *Substd. phenylamidines with antithrombotic action*. DE 19833105, WO 0005207.

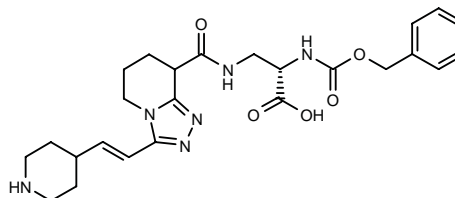
286155

3-(S)-[3-[(E)-2-(4-Piperidiny)vinyl]-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyridin-8-ylcarboxamido]-3-(3-pyridyl)propionic acid



C22 H28 N6 O3; Mol wt: 424.5022

ACTION – Antithrombotic agent and platelet aggregation inhibitor, a gpIIb/IIIa (fibrinogen) receptor antagonist. *In vitro*, compound was shown to inhibit fibrinogen binding to gpIIb/IIIa ($IC_{50} = 0.14$ nM), as well as thrombin-induced aggregation of human platelet-rich plasma ($IC_{50} = 0.030$ μ M). In addition, it exhibited potent effects when tested *ex vivo* in dogs, giving > 50% inhibition of ADP-induced platelet aggregation for 150 and 360 min following administration of 0.1 mg/kg i.v. and 1 mg/kg p.o., respectively. Another specifically claimed compound from this series of triazolopyridines is:



286156: C25 H32 N6 O5

SOURCE – Ortho-McNeil.

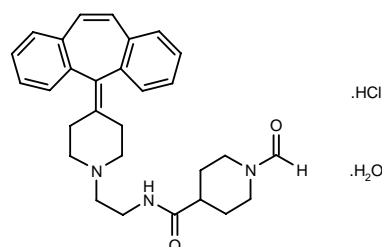
REFERENCES

1. Hoekstra, W.J. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Triazolopyridines for the treatment of thrombosis disorders*. WO 0006570.

AT-1015

283381

N-[2-[4-(Dibenzo[a,d]cyclohepten-5-ylidene)piperidin-1-yl]ethyl]-1-formylpiperidine-4-carboxamide hydrochloride hydrate



C29 H33 N3 O2 . HCl . H2O; Mol wt: 510.0744

ACTION – Antithrombotic agent, a potent 5-HT_{2A} receptor antagonist with pK_b values of 9.04 and 8.61 for antagonizing contractions induced by 5-HT and Me-5-HT, respectively, in endothelium-denuded porcine coronary arteries.

SOURCE – Ajinomoto.

REFERENCES

1. Kubo, M. et al. (Ajinomoto Co., Inc.) *Crystals of piperidine derivs., intermediates for production of the same, and process for producing the same.* EP 0770602.

2. Makino, S. et al. (Ajinomoto Co., Inc.) *Piperidine derivates and anti-platelet agents containing the same.* CA 2147429, EP 0682015, JP 1996003135, JP 1999246526, US 5932593.

3. Gong, H. et al. *Inhibitory effects of AT-1015, a newly synthesized 5-HT_{2A} receptor antagonist on contraction of porcine coronary arteries induced by 5-HT.* Jpn J Pharmacol 2000, 82(Suppl. 1): Abst P-256.

4. Kihara, H. et al. *AT-1015, a novel long acting serotonin (5-HT)_{2A} receptor antagonist, prevents arterial thrombus formation without prolongation of bleeding time in rats.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P52.45.

5. Kihara, H. et al. *Effect of AT-1015, a novel serotonin (5-HT)₂ receptor antagonist, on laurate induced peripheral disease model in rats.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-316.

6. Koganei, H. et al. *Anti-thrombotic effect and bleeding risk of AT-1015, a novel serotonin (5-HT)₂ receptor antagonist.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-315.

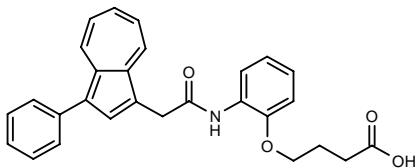
7. *Ajinomoto expands European and U.S. development efforts.* DailyDrugNews.com (Daily Essentials) 1999, Nov 17.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

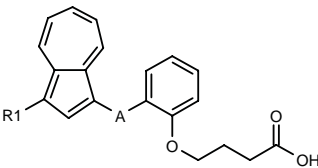
286028

4-[2-[2-(3-Phenylazulen-1-yl)acetamido]phenoxy]butyric acid



C28 H25 N O4; Mol wt: 439.5085

ACTION – Potent steroid 5 α -reductase inhibitor (IC₅₀ = 0.0028 μ M against rat prostate enzyme), a representative compound from a series of azulene derivatives, wherein the following are also included:



Compound	R1	A	Formula
286029	4-i-Bu-PhCH2	-CONH-	C ₃₂ H ₃₃ NO ₄
286030	Ph	-CONH-	C ₂₇ H ₂₃ NO ₄
286031	4-Me-Ph	-CONH-	C ₂₈ H ₂₅ NO ₄
286032	4-Cl-Ph	-CONH-	C ₂₇ H ₂₂ ClNO ₄
286033	4-MeO-Ph	-CONH-	C ₂₈ H ₂₆ NO ₅
286036	Ph	-NHCO-	C ₂₇ H ₂₃ NO ₄

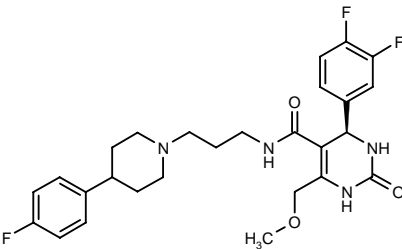
SOURCE – Kotobuki.

REFERENCES

1. Tomiyama, T. et al. (Kotobuki Pharmaceutical Co., Ltd.) *Azulene derivs. having steroid 5 α -reductase inhibitory activity, their preparation method, and agents containing them.* JP 2000007611.

286154

(-)-4(*R*)-(3,4-Difluorophenyl)-*N*-[3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl]-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



C27 H31 F3 N4 O3; Mol wt: 516.5609

ACTION – Potent and selective human α_{1A} -adrenoceptor antagonist with high affinity for this receptor (K_i = 0.24 nM) and at least 50-fold selectivity over α_{1B} - (K_i = 41 nM) and α_{1D} -adrenoceptors (K_i = 260 nM) in binding assays, and thus expected to exhibit reduced side effects related to peripheral adrenergic blockade such as hypotension, syncope and lethargy as compared to nonselective α_1 -adrenoceptor antagonists. The compound was about 4 times as potent as terazosin in inhibiting phenylephrine-induced increases in intraurethral pressure in anesthetized dogs (AD₅₀ = 25 μ g/kg i.v.), while having significantly less effect on diastolic blood pressure (decrease of 20 mmHg at > 300 μ g/kg i.v.). In conscious dogs, it had a similar duration of action as regards inhibition of phenylephrine-induced increases in intraurethral pressure as terazosin but at half the dose (100 μ g/kg i.v. vs. 200 μ g/kg i.v.). It also showed good oral bioavailability in rats (21%) and dogs (40%). Potentially useful for providing acute relief in males suffering from benign prostatic hyperplasia by virtue of its ability to relax lower urinary tract tissue.

ACTION – Antithrombotic agent, a potent 5-HT_{2A} receptor antagonist with pK_b values of 9.04 and 8.61 for antagonizing contractions induced by 5-HT and Me-5-HT, respectively, in endothelium-denuded porcine coronary arteries.

SOURCE – Ajinomoto.

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1. Kubo, M. et al. (Ajinomoto Co., Inc.) *Crystals of piperidine derivs., intermediates for production of the same, and process for producing the same.* EP 0770602.

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6. Koganei, H. et al. *Anti-thrombotic effect and bleeding risk of AT-1015, a novel serotonin (5-HT)₂ receptor antagonist.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-315.

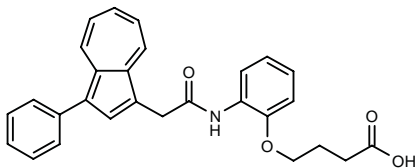
7. *Ajinomoto expands European and U.S. development efforts.* DailyDrugNews.com (Daily Essentials) 1999, Nov 17.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

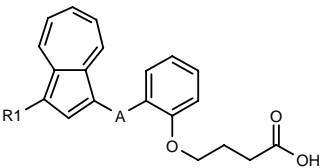
286028

4-[2-[2-(3-Phenylazulen-1-yl)acetamido]phenoxy]butyric acid



C28 H25 N O4; Mol wt: 439.5085

ACTION – Potent steroid 5 α -reductase inhibitor (IC₅₀ = 0.0028 μ M against rat prostate enzyme), a representative compound from a series of azulene derivatives, wherein the following are also included:



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286031	4-Me-Ph	-CONH-	C ₂₈ H ₂₅ NO ₄
286032	4-Cl-Ph	-CONH-	C ₂₇ H ₂₂ ClNO ₄
286033	4-MeO-Ph	-CONH-	C ₂₈ H ₂₆ NO ₅
286036	Ph	-NHCO-	C ₂₇ H ₂₃ NO ₄

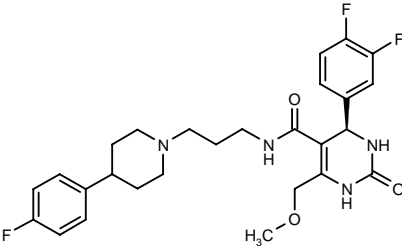
SOURCE – Kotobuki.

REFERENCES

1. Tomiyama, T. et al. (Kotobuki Pharmaceutical Co., Ltd.) *Azulene derivs. having steroid 5 α -reductase inhibitory activity, their preparation method, and agents containing them.* JP 2000007611.

286154

(–)-4(*R*)-(3,4-Difluorophenyl)-*N*-[3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl]-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



C27 H31 F3 N4 O3; Mol wt: 516.5609

ACTION – Potent and selective human α_{1A} -adrenoceptor antagonist with high affinity for this receptor (K_i = 0.24 nM) and at least 50-fold selectivity over α_{1B} - (K_i = 41 nM) and α_{1D} -adrenoceptors (K_i = 260 nM) in binding assays, and thus expected to exhibit reduced side effects related to peripheral adrenergic blockade such as hypotension, syncope and lethargy as compared to nonselective α_1 -adrenoceptor antagonists. The compound was about 4 times as potent as terazosin in inhibiting phenylephrine-induced increases in intraurethral pressure in anesthetized dogs (AD₅₀ = 25 μ g/kg i.v.), while having significantly less effect on diastolic blood pressure (decrease of 20 mmHg at > 300 μ g/kg i.v.). In conscious dogs, it had a similar duration of action as regards inhibition of phenylephrine-induced increases in intraurethral pressure as terazosin but at half the dose (100 μ g/kg i.v. vs. 200 μ g/kg i.v.). It also showed good oral bioavailability in rats (21%) and dogs (40%). Potentially useful for providing acute relief in males suffering from benign prostatic hyperplasia by virtue of its ability to relax lower urinary tract tissue.

SOURCES – Merck & Co.; Synaptic.

REFERENCES

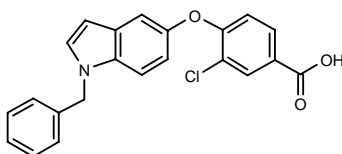
1. Barrow, J.C. et al. (Merck & Co., Inc.) α_{1A} Adrenergic receptor antagonists. WO 0006565.

2. Rittle, K. et al. Dihydropyrimidinone C-5 amides as potent and selective α_{1A} receptor antagonists. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 90.

YM-32906¹⁻³

220989

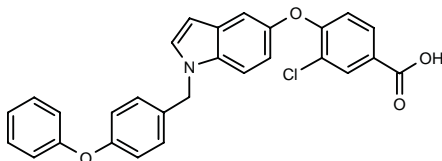
4-(1-Benzylindol-5-yloxy)-3-chlorobenzoic acid



C22 H16 Cl N O3; Mol wt: 377.8254

M.p. 158-9 °C.

ACTION – Potent inhibitor of human steroid 5 α -reductase (IC_{50} = 0.44 nM) proven inactive against rat enzyme (IC_{50} > 300 nM). Potentially useful for the treatment of androgen-related disorders associated with elevated levels of dihydrotestosterone such as benign prostatic hyperplasia and skin disorders including acne, male pattern baldness and hirsutism. Another related compound from this series of indole derivatives is:



286555^{2,3}: C28 H20 Cl N O4

SOURCE – Yamanouchi.

REFERENCES

1. Hara, H. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Benzoic acid derivs. or their salts*. JP 1994312976.

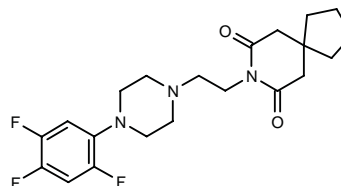
2. Igarashi, D. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Benzoic acid derivs. or their salts*. JP 1995145147.

3. Igarashi, S. et al. *A novel class of inhibitors for human steroid 5 α -reductase: Synthesis and biological evaluation of indole derivatives. II*. Chem Pharm Bull 2000, 48(3): 382.

TREATMENT OF URINARY INCONTINENCE

285560

8-[2-[4-(2,4,5-Trifluorophenyl)piperazin-1-yl]ethyl]-8-azaspiro[4.5]decane-7,9-dione



C21 H26 F3 N3 O2; Mol wt: 409.4494

ACTION – Potent and selective α_{1D} -adrenoceptor antagonist (pK_i = 8.7) with selectivity over α_{1A} - and α_{1B} -adrenoceptors (pK_i = 5.4 and 6.4, respectively) and 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors (pK_i = 6.4, 5.3 and 6.1, respectively) in binding studies using cloned human receptors. In functional studies, it also showed high potency and selectivity as an α_{1D} -adrenoceptor antagonist, giving pK_B values for inhibition of phenylephrine-induced contractions in rat thoracic aorta (α_{1D}), rat epididymal vas deferens (α_{1A}) and rat spleen (α_{1B}) of 8.5 ± 0.2 , 5.2 ± 0.2 and 6.7 ± 0.2 , respectively. While reported to be effective at reducing blood pressure in hypertensive animals, compound exhibited a minor reduction in blood pressure in anesthetized normotensive rats and it did not exhibit any blood pressure-lowering activity in conscious normotensive animals, thus suggesting the feasibility of its use in normotensive individuals without unwanted cardiovascular side effects. Potentially useful in the treatment of α_{1D} -adrenoceptor-mediated disorders such as bladder instability associated with urinary incontinence, Raynaud's disease and hypertension.

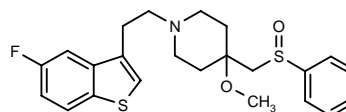
SOURCE – Synaptic.

REFERENCES

1. Konkel, M. et al. (Synaptic Pharmaceutical Corp.) *Cpds. specific for the human α_{1D} adrenergic receptor and uses thereof*. WO 0004012.

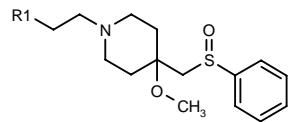
286262

1-[2-(5-Fluorobenzothiophen-3-yl)ethyl]-4-methoxy-4-(phenylsulfinylmethyl)piperidine



C23 H26 F N O2 S2; Mol wt: 431.5934

ACTION – Tachykinin NK₂ antagonist, as demonstrated in a functional assay in rabbit pulmonary artery preparations, with potential in the treatment of urinary disorders, gastrointestinal disorders, emesis, anxiety, asthma, rheumatoid arthritis and pain. Other compounds from this series of cyclic amine derivatives include the following:



Compound	R1	Formula
286263	3-NO2-Ph	C ₂₁ H ₂₆ N ₂ O ₄ S
286264	3,5-(Cl)2-Ph	C ₂₁ H ₂₅ Cl ₂ NO ₂ S
286265	5-Cl-3-benzothienyl	C ₂₃ H ₂₆ ClNO ₂ S ₂

Certain exemplified compounds demonstrated NK₁ receptor-antagonist activity.

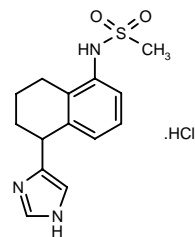
SOURCE – Kyorin.

REFERENCES

1. Takadoi, M. et al. (Kyorin Pharmaceutical Co., Ltd.) *Cyclic amine derivs. and process for the preparation thereof*. JP 2000103782, WO 0006544.

286332

N-[5-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulfonamide hydrochloride



C14 H17 N3 O2 S . HCl; Mol wt: 327.8342

ACTION – Selective α_{1A} -adrenoceptor agonist with potential in the treatment of urinary incontinence and ejaculatory dysfunction. *In vitro*, compound was shown to bind to rat α_{1A} -, hamster α_{1B} - and rat α_{1D} -adrenoceptors with respective K_i values of 176, 4620 and 1590 nM, while in functional assays evaluating its ability to stimulate contractions of rabbit urethra (α_{1A}), rat spleen (α_{1B}) and rat aorta (α_{1D}), it gave respective pD_2 values of 6.35, 5.29 and 4.37. When tested *in vivo* in anesthetized telemetric dogs, compound was shown to increase intraurethral pressure (IUP; $ED_5 = 25.5$ nmol/kg i.v.) at doses having little or no effect on mean arterial blood pressure (MAP; $ED_{20} = 102$ nmol/kg). In addition, increasing doses (3-300 nmol/kg i.v.) resulted in corresponding increases in urethral pressure in anesthetized dogs.

SOURCE – Abbott.

REFERENCES

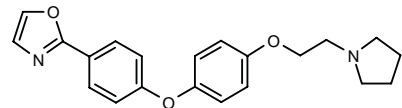
1. Altenbach, R.J. et al. (Abbott Laboratories Inc.) *Imidazoles and related cpds. as α_{1A} agonists*. WO 0007997.

GASTROINTESTINAL DRUGS

INFLAMMATORY BOWEL DISEASE THERAPY

285843

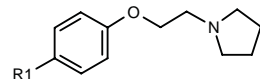
2-[4-[4-[2-(1-Pyrrolidiny)ethoxy]phenoxy]phenyl]oxazole



C21 H22 N2 O3; Mol wt: 350.4158

White solid.

ACTION – Nonpeptide human LTA₄ hydrolase inhibitor ($IC_{50} = 0.59$ and 0.55 μ M against recombinant and human whole blood LTA₄ hydrolase, respectively) found to inhibit mouse blood LTA₄ hydrolase by 93% after oral administration at 10 mg/kg. Potentially useful for the treatment of inflammatory states including inflammatory bowel disease, psoriasis, rheumatoid arthritis, gout and asthma. Other related compounds in this series of 1-[2-(4-phenylphenoxy)ethyl]pyrrolidines are:



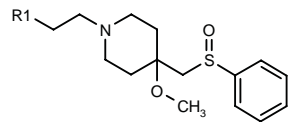
Compound	R1	Formula
SC-22716 [285824]	Ph	C ₁₈ H ₂₁ NO
285844	4-(4,5-dihydrooxazolyl-2-yl)-PhO	C ₂₁ H ₂₄ N ₂ O ₃

SOURCE – Pharmacia.

REFERENCES

1. Chen, B.B. et al. (G.D. Searle & Co.) *LTA4 hydrolase inhibitors*. EP 0970060, US 5925654, WO 9840364.

2. Penning, T.D. et al. *Structure-activity relationship studies on 1-[2-(4-phenylphenoxy)ethyl]pyrrolidine (SC-22716), a potent inhibitor of leukotriene A4 (LTA4) hydrolase*. J Med Chem 2000, 43(3): 721.



Compound	R1	Formula
286263	3-NO2-Ph	C ₂₁ H ₂₆ N ₂ O ₄ S
286264	3,5-(Cl)2-Ph	C ₂₁ H ₂₅ Cl ₂ NO ₂ S
286265	5-Cl-3-benzothienyl	C ₂₃ H ₂₆ ClNO ₂ S ₂

Certain exemplified compounds demonstrated NK₁ receptor-antagonist activity.

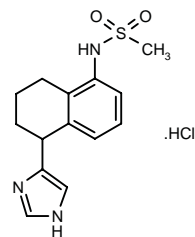
SOURCE – Kyorin.

REFERENCES

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286332

N-[5-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulfonamide hydrochloride



C14 H17 N3 O2 S . HCl; Mol wt: 327.8342

ACTION – Selective α_{1A} -adrenoceptor agonist with potential in the treatment of urinary incontinence and ejaculatory dysfunction. *In vitro*, compound was shown to bind to rat α_{1A} -, hamster α_{1B} - and rat α_{1D} -adrenoceptors with respective K_i values of 176, 4620 and 1590 nM, while in functional assays evaluating its ability to stimulate contractions of rabbit urethra (α_{1A}), rat spleen (α_{1B}) and rat aorta (α_{1D}), it gave respective pD_2 values of 6.35, 5.29 and 4.37. When tested *in vivo* in anesthetized telemetric dogs, compound was shown to increase intraurethral pressure (IUP; $ED_5 = 25.5$ nmol/kg i.v.) at doses having little or no effect on mean arterial blood pressure (MAP; $ED_{20} = 102$ nmol/kg). In addition, increasing doses (3-300 nmol/kg i.v.) resulted in corresponding increases in urethral pressure in anesthetized dogs.

SOURCE – Abbott.

REFERENCES

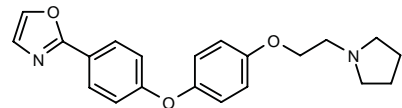
1. Altenbach, R.J. et al. (Abbott Laboratories Inc.) *Imidazoles and related cpds. as α_{1A} agonists*. WO 0007997.

GASTROINTESTINAL DRUGS

INFLAMMATORY BOWEL DISEASE THERAPY

285843

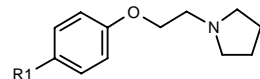
2-[4-[4-[2-(1-Pyrrolidiny)ethoxy]phenoxy]phenyl]oxazole



C21 H22 N2 O3; Mol wt: 350.4158

White solid.

ACTION – Nonpeptide human LTA₄ hydrolase inhibitor ($IC_{50} = 0.59$ and 0.55 μ M against recombinant and human whole blood LTA₄ hydrolase, respectively) found to inhibit mouse blood LTA₄ hydrolase by 93% after oral administration at 10 mg/kg. Potentially useful for the treatment of inflammatory states including inflammatory bowel disease, psoriasis, rheumatoid arthritis, gout and asthma. Other related compounds in this series of 1-[2-(4-phenylphenoxy)ethyl]pyrrolidines are:



Compound	R1	Formula
SC-22716 [285824]	Ph	C ₁₈ H ₂₁ NO
285844	4-(4,5-dihydrooxazolyl-2-yl)-PhO	C ₂₁ H ₂₄ N ₂ O ₃

SOURCE – Pharmacia.

REFERENCES

1. Chen, B.B. et al. (G.D. Searle & Co.) *LTA4 hydrolase inhibitors*. EP 0970060, US 5925654, WO 9840364.

2. Penning, T.D. et al. *Structure-activity relationship studies on 1-[2-(4-phenylphenoxy)ethyl]pyrrolidine (SC-22716), a potent inhibitor of leukotriene A4 (LTA4) hydrolase*. J Med Chem 2000, 43(3): 721.

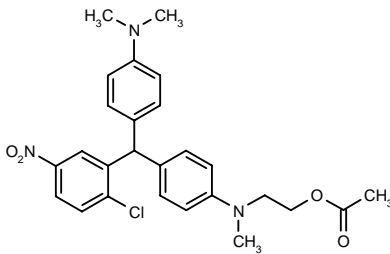
ENDOCRINE DRUGS

ADRENOCORTICAL DYSFUNCTION THERAPY

286299

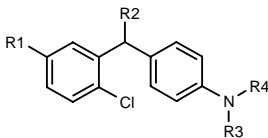
Acetic acid 2-[N-[4-[1-(2-chloro-5-nitrophenyl)-1-[4-(dimethylamino)phenyl]methyl]phenyl]-N-methylamino]ethyl ester

4-[N-(2-Acetoxyethyl)-N-methylamino]-2'-chloro-4''-(dimethylamino)-5'-nitrotriphenylmethane



C26 H28 Cl N3 O4; Mol wt: 481.9772

ACTION – Selective glucocorticoid receptor modulator with potential in the treatment of immune, autoimmune, inflammatory, adrenal imbalance, cognitive and behavioral disorders. In binding assays, compound exhibited K_i values of 167, 1084, > 10,000, > 10,000 and > 10,000 nM for the human glucocorticoid, progesterone, mineralocorticoid, androgen and estrogen- α receptors, respectively. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
286300	NO2	4-(MeNH)-Ph	H	Me	C ₂₁ H ₂₀ ClN ₃ O ₂
286301	Cl	4-N(Me)2-Ph	Me	Me	C ₂₃ H ₂₄ Cl ₂ N ₂
286302	Cl	4-(MeNH)-Ph	H	Me	C ₂₁ H ₂₀ Cl ₂ N ₂
286303	NO2	4-[AcOCH2CH2N(Me)]-Ph	Me	(CH2)2OAc	C ₂₉ H ₃₂ ClN ₃ O ₆
286304	NO2	4-[OHCH2CH2N(Me)]-Ph	Me	CH2CH2OH	C ₂₈ H ₂₈ ClN ₃ O ₄
286305	NO2	4-(PhCH2NH)-Ph	H	CH2Ph	C ₃₃ H ₂₈ ClN ₃ O ₂
286306	NO2	4-(MeNH)-Ph	Me	Me	C ₂₂ H ₂₂ ClN ₃ O ₂
286307	NO2	4-N(Me)2-Ph	Me	CH2CH2OH	C ₂₄ H ₂₆ ClN ₃ O ₃
286308	NO2	4-(MeNH)-Ph	Me	(CH2)2OAc	C ₂₈ H ₂₆ ClN ₃ O ₄
286309	NO2	OPh	Me	Me	C ₂₁ H ₁₉ ClN ₂ O ₃
286310	NO2	SPh	Me	Me	C ₂₁ H ₁₉ ClN ₂ O ₂ S

SOURCE – Abbott.

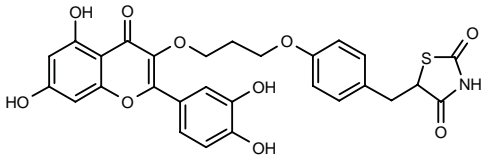
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1. Coghlan, M.J. et al. (Abbott Laboratories Inc.) *Glucocorticoid-selective agents*. WO 0006137.

ANTIDIABETIC DRUGS

286021

5-[4-[3-[2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yloxy]propoxy]benzyl]thiazolidine-2,4-dione



C28 H23 N O10 S; Mol wt: 565.5527

ACTION – Peroxisome proliferator-activated receptor PPAR γ agonist with potential in the treatment of diabetes, malignant and nonmalignant proliferative diseases including prostate cancer, breast cancer, psoriasis and acne, and certain cardiovascular disorders including hypertension and occlusive vascular diseases. A representative compound from a series of thiazolidinedione derivatives.

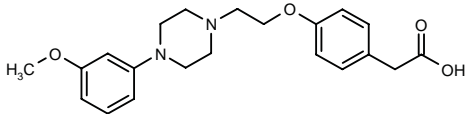
SOURCE – University of Mississippi, Oxford, MS (US).

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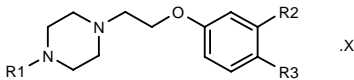
286283

2-[4-[2-[4-(3-Methoxyphenyl)piperazin-1-yl]ethoxy]-phenyl]acetic acid



C21 H26 N2 O4; Mol wt: 370.4464

ACTION – Hypoglycemic and hypolipidemic agent proven to reduce glycemia by 24 and 34% on days 1 and 4, respectively, at a dose of 200 mg/kg/day p.o in non-insulin-dependent streptozotocin-diabetic rats; it was also shown to decrease total cholesterol and triglycerides in these animals. Potentially useful in the treatment of pathologies associated with insulin resistance syndrome such as diabetes, dyslipidemia, obesity, arterial hypertension, neuropathy, retinopathy and atherosclerosis. A representative compound from a series of piperazine derivatives, wherein the following are also included:



Compound	R1	R2	R3	X	Formula
286284	3-MeO-Ph	CH2CO2H	H		C ₂₁ H ₂₆ N ₂ O ₄
286285	3-Cl-Ph	H	CH2CO2H		C ₂₀ H ₂₃ ClN ₂ O ₃
286286	3-(PhO)-Ph	H	CH2CO2H		C ₂₆ H ₂₈ N ₂ O ₄
286287	2-MeO-Ph	H	CH2CO2H	2HCl	C ₂₁ H ₂₆ N ₂ O ₄ ·2HCl
286288	3-CF3-Ph	H	CH2CO2H		C ₂₁ H ₂₃ F ₃ N ₂ O ₃
286289	2-pyrimidinyl	H	CH2CO2H		C ₁₈ H ₂₂ N ₄ O ₃

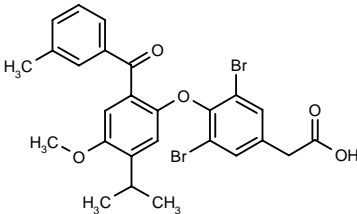
SOURCE – Merck KGaA.

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1. Moinet, G. et al. (Merck Patent GmbH) *Antidiabetic piperazine derivs., processes for their preparation and compsns. containing them.* FR 2781797, WO 0006558.

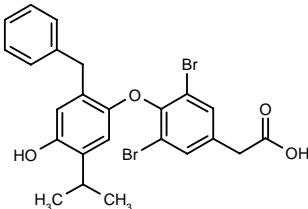
286333

2-[3,5-Dibromo-4-[5-isopropyl-4-methoxy-2-(3-methyl-benzoyl)phenoxy]phenyl]acetic acid



C26 H24 Br2 O5; Mol wt: 576.2786

ACTION – Liver-selective glucocorticoid receptor antagonist and thyroid hormone receptor agonist with potential in the treatment of metabolic disorders or disorders dependent upon the expression of a gluco-corticoid or thyroid hormone receptor-regulated genes such as diabetes, Cushing’s syndrome, inflammation, obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, thyroid cancer, glaucoma and congestive heart failure. Another specifically claimed compound is:



286334: C24 H22 Br2 O4

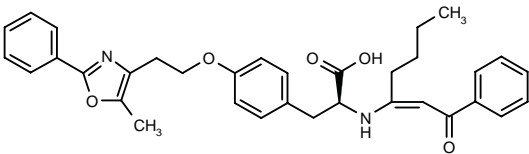
SOURCE – Karo Bio.

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1. Apelqvist, T. et al. (Karo Bio AB) *Glucocorticoid and thyroid hormone receptor ligands for the treatment of metabolic disorders.* WO 0007972.

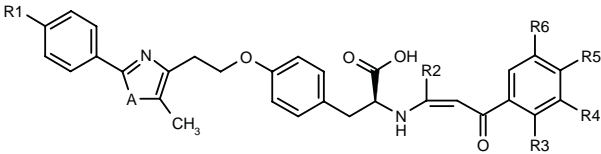
286461

2(S)-[1-Butyl-3-oxo-3-phenyl-1(Z)-propenylamino]-3-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl]propionic acid



C34 H36 N2 O5; Mol wt: 552.6674

ACTION – Dual human peroxisome proliferator-activated receptor PPARγ and PPARα activator with potential in the treatment or prevention of hyperglycemia, dyslipidemia and type II diabetes mellitus including associated diabetic dyslipidemia. Compound showed at least 50% activation of human PPARα and PPARγ *in vitro* at concentrations of 0.1 μM or less, and markedly reduced blood glucose levels in Zucker diabetic rats following p.o. administration. A representative compound from a series of substituted oxazoles and thiazoles, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	R6	A	Formula
286464	H	Me	F	F	F	H	O	C ₃₁ H ₂₇ F ₃ N ₂ O ₅
286465	H	Me	F	H	F	F	O	C ₃₁ H ₂₇ F ₃ N ₂ O ₅
286466	H	Et	H	H	H	H	O	C ₃₂ H ₃₂ N ₂ O ₅
286467	F	CF3	H	H	H	H	S	C ₃₁ H ₂₆ F ₄ N ₂ O ₄ S
286468	H	Pr	H	H	H	H	O	C ₃₃ H ₃₄ N ₂ O ₅
286469	H	CF3	H	H	H	H	O	C ₃₁ H ₂₇ F ₃ N ₂ O ₅

SOURCE – Glaxo Wellcome.

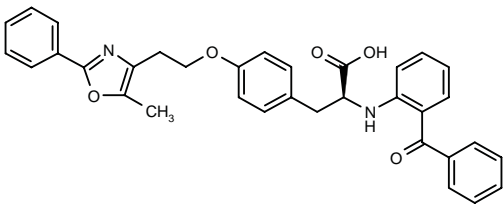
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1. Collins, J.L. et al. (Glaxo Group Ltd.) *Substd. oxazoles and thiazoles derivs. as hPPAR γ and hPPAR α activators.* WO 0008002.

GI-262570*

255618

2(S)-(2-Benzoylphenylamino)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)ethoxy]phenyl]propionic acid



C34 H30 N2 O5; Mol wt: 546.6200

ACTION – Potent and selective, nonthiazolidinedione peroxisome proliferator-activated receptor PPAR γ agonist with low nanomolar binding affinity for this receptor (pK_i = 8.94) and subnanomolar *in vitro* functional potency in a cell-based transactivation assay (pEC_{50} = 9.47) and as regards lipogenic activity (pEC_{50} = 8.83 in C3H10T1/2 stem cells). Compound was at least 500-fold selective for PPAR γ over PPAR α receptors with respect to both receptor affinity and *in vitro* functional agonist activity, and did not show activity at PPAR δ receptors at concentrations up to 10 μ M. In Zucker diabetic fatty rats, it was able to lower plasma glucose, serum triglycerides and nonesterified free fatty acids (65, 77 and 77%, respectively) when dosed orally at 5 mg/kg for 14 days. Currently in phase III clinical trials for the treatment of type II diabetes.

SOURCE – Glaxo Wellcome.

REFERENCES

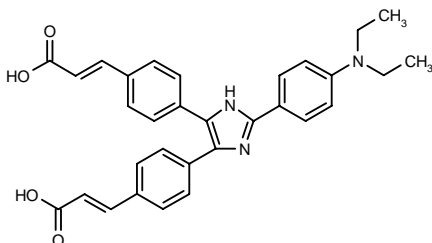
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- Glaxo Wellcome outlines key future products at NYC conference. DailyDrugNews.com (Daily Essentials) 1999, Nov 2.
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*Identified compound **255618** Drug Data Rep 1998, 020(01): 0051.

OC-060-062¹⁻³

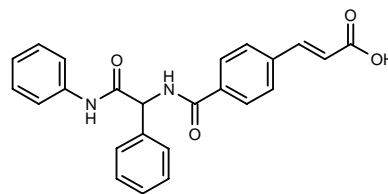
286883

3,3'-[2-[4-(Diethylamino)phenyl-1*H*-imidazole-4,5-diyl]di-4,1-phenylene]bis[2(*E*)-propenoic acid]



C31 H29 N3 O4; Mol wt: 507.5871

ACTION – Potential antidiabetic agent, an inhibitor of protein-tyrosine-phosphatase PTP1B (IC_{50} = 0.05 μ M) with 60-fold selectivity over PTP ϵ (IC_{50} = 3 μ M). Another related compound is:



OC-868393 [**286884**]: C24 H20 N2 O4

SOURCE – Ontogen.

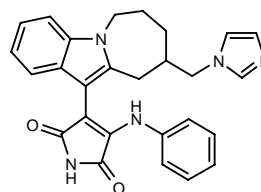
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TREATMENT OF DIABETIC COMPLICATIONS

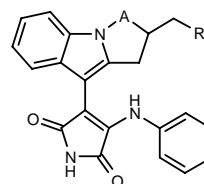
286238

3-[9-(1*H*-Imidazol-1-ylmethyl)-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indol-11-yl]-4-(phenylamino)-2,5-dihydro-1*H*-pyrrole-2,5-dione

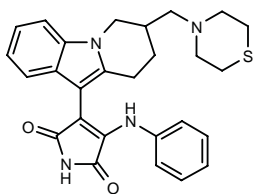


C27 H25 N5 O2; Mol wt: 451.5275

ACTION – A selective protein kinase C β (PKC β) inhibitor, as demonstrated by IC_{50} values of 0.041 and > 10 μ M, respectively, against recombinant PKC β II and PKC α enzymes (ratio α/β = 244). Potentially useful in the treatment of PKC-mediated conditions, particularly diabetic complications. Other compounds within this series of disubstituted maleimide derivatives include the following:



Compound	R1	A	Isomer	Formula
286239	OH	-(CH2)3-		C ₂₄ H ₂₃ N ₃ O ₃
286240	N(Me) ₂	-(CH2)3-		C ₂₆ H ₂₈ N ₄ O ₂
286241	4-thiomorpholinyl	-CH2-		C ₂₆ H ₂₈ N ₄ O ₂ S
286243	OMe	-CH2-	S	C ₂₃ H ₂₁ N ₃ O ₃



286242: C₂₇ H₂₈ N₄ O₂ S

SOURCE – Japan Tobacco.

REFERENCES

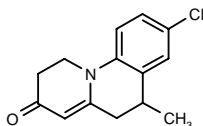
1. Inaba, T. et al. (Japan Tobacco Inc.) *Disubstd. maleimide cpds. and medicinal utilization thereof*. JP 2000109479, WO 0006564.

DERMATOLOGIC DRUGS

ACNE THERAPY

286081

8-Chloro-6-methyl-2,3,5,6-tetrahydro-1*H*-benzo[*c*]-quinolizin-3-one



C₁₄ H₁₄ Cl N O; Mol wt: 247.7236

ACTION – Potent and selective inhibitor of human steroid 5 α -reductase type 1 (IC₅₀ = 14.4 nM) potentially useful for the treatment of skin disorders including acne, alopecia, male pattern baldness and hirsutism.

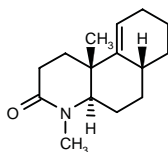
SOURCE – Università degli Studi di Firenze, Firenze (IT).

REFERENCES

1. Guarna, A. et al. *Synthesis of 8-chloro-benzo[*c*]quinolizin-3-ones as potent and selective inhibitors of human steroid 5 α -reductase 1*. Bioorg Med Chem Lett 2000, 10(4): 353.

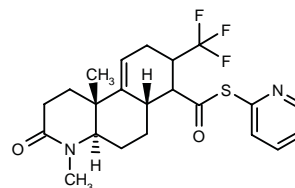
286164

(4a*R**,6a*R**,10b*R**)-4,10b-Dimethyl-1,2,3,4,4a,5,6,6a,7,8,9,10b-dodecahydrobenzo[*f*]quinolin-3-one

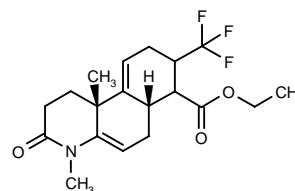


C₁₅ H₂₃ N O; Mol wt: 233.3527

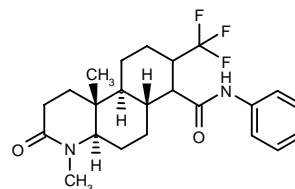
ACTION – 5 α -Reductase inhibitor with selectivity for type 1 isoform and potential in the treatment of hyperandrogenic conditions such as acne vulgaris, seborrhea, androgenic alopecia, female hirsutism, benign prostatic hyperplasia, prostatitis, sweat-related disorders, polycystic ovary syndrome and prostate cancer. Other specifically claimed compounds from this series of tricyclic compounds having the natural steroidal *trans-anti-trans* relative configuration at the A, B and C ring structure include the following:



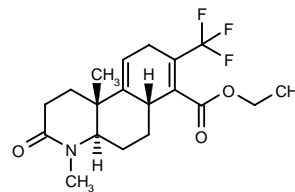
286165: C₂₂ H₂₅ F₃ N₂ O₂ S



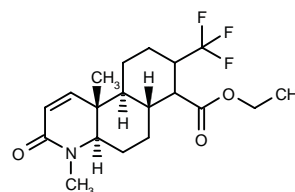
286166: C₁₉ H₂₄ F₃ N O₃



286167: C₂₃ H₂₉ F₃ N₂ O₂



286168: C₁₉ H₂₄ F₃ N O₃

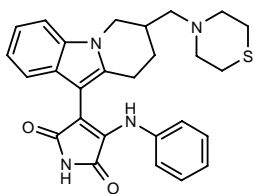


286169: C₁₉ H₂₆ F₃ N O₃

SOURCE – Merck & Co.

REFERENCES

1. Von Langen, D. et al. (Merck & Co., Inc.) *Tricyclic cpds*. US 6048869, WO 0006167.



286242: C₂₇ H₂₈ N₄ O₂ S

SOURCE – Japan Tobacco.

REFERENCES

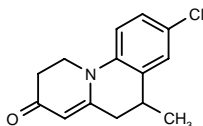
1. Inaba, T. et al. (Japan Tobacco Inc.) *Disubstd. maleimide cpds. and medicinal utilization thereof*. JP 2000109479, WO 0006564.

DERMATOLOGIC DRUGS

ACNE THERAPY

286081

8-Chloro-6-methyl-2,3,5,6-tetrahydro-1*H*-benzo[*c*]-quinolizin-3-one



C₁₄ H₁₄ Cl N O; Mol wt: 247.7236

ACTION – Potent and selective inhibitor of human steroid 5 α -reductase type 1 (IC₅₀ = 14.4 nM) potentially useful for the treatment of skin disorders including acne, alopecia, male pattern baldness and hirsutism.

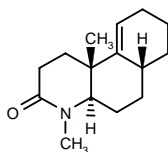
SOURCE – Università degli Studi di Firenze, Firenze (IT).

REFERENCES

1. Guarna, A. et al. *Synthesis of 8-chloro-benzo[*c*]quinolizin-3-ones as potent and selective inhibitors of human steroid 5 α -reductase 1*. Bioorg Med Chem Lett 2000, 10(4): 353.

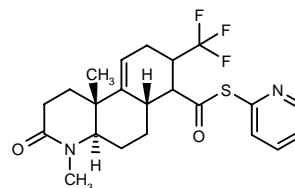
286164

(4a*R**,6a*R**,10b*R**)-4,10b-Dimethyl-1,2,3,4,4a,5,6,6a,7,8,9,10b-dodecahydrobenzo[*f*]quinolin-3-one

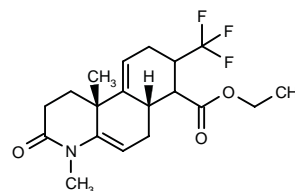


C₁₅ H₂₃ N O; Mol wt: 233.3527

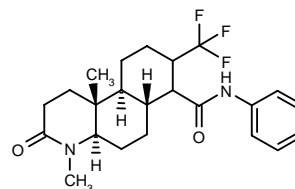
ACTION – 5 α -Reductase inhibitor with selectivity for type 1 isoform and potential in the treatment of hyperandrogenic conditions such as acne vulgaris, seborrhea, androgenic alopecia, female hirsutism, benign prostatic hyperplasia, prostatitis, sweat-related disorders, polycystic ovary syndrome and prostate cancer. Other specifically claimed compounds from this series of tricyclic compounds having the natural steroidal *trans-anti-trans* relative configuration at the A, B and C ring structure include the following:



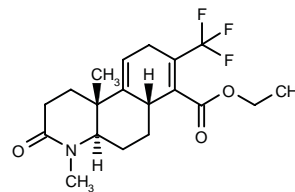
286165: C₂₂ H₂₅ F₃ N₂ O₂ S



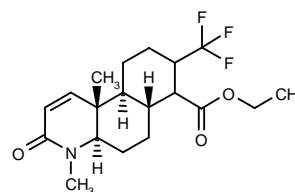
286166: C₁₉ H₂₄ F₃ N O₃



286167: C₂₃ H₂₉ F₃ N₂ O₂



286168: C₁₉ H₂₄ F₃ N O₃



286169: C₁₉ H₂₆ F₃ N O₃

SOURCE – Merck & Co.

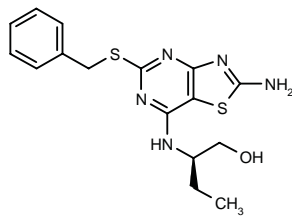
REFERENCES

1. Von Langen, D. et al. (Merck & Co., Inc.) *Tricyclic cpds*. US 6048869, WO 0006167.

ANTIPSORIATICS

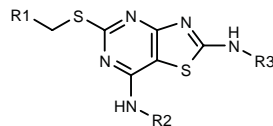
286526

2(R)-[2-Amino-5-(benzylsulfanyl)thiazolo[4,5-*d*]pyrimidin-7-ylamino]butan-1-ol

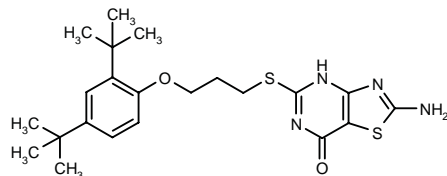


C16 H19 N5 O S2; Mol wt: 361.4921

ACTION – Chemokine, particularly CXCR2, receptor modulator for use in the treatment of inflammatory and immune disorders, especially psoriasis. Compound was shown to inhibit the binding of [¹²⁵I]-IL-8 in human CXCR2-expressing HEK293 cells (IC₅₀ < 10 μM) and proved to be an antagonist of this receptor in human neutrophils. Other specifically claimed compounds from this series of thiazolopyrimidine derivatives include the following:



Compound	R1	R2	R3	Formula
286529	3-(PhO)-Ph	(R)-i-BuCH(CH2OH)	H	C ₁₈ H ₂₃ N ₅ O ₂ S ₂
286533	2,3-(F)2-Ph	CH2C(Me)2OH	H	C ₁₆ H ₁₇ F ₂ N ₅ OS ₂
286536	2,3-(F)2-Ph	4-imidazolyl-CH2CH2	H	C ₁₇ H ₁₅ F ₂ N ₇ S ₂
286540	Ph	C(Me)2CH2OH	(CH2)4Ph	C ₂₆ H ₃₁ N ₅ OS ₂
286542	Ph	C(Me)2CH2OH	CH(Ph)2	C ₂₉ H ₂₉ N ₅ OS ₂
286543	Ph	(CH2)5OH	4-imidazolyl-CH2CH2	C ₂₂ H ₂₇ N ₇ OS ₂
286544	Ph	CH2CH2OMe	2-thienyl-CH2CH2	C ₂₁ H ₂₃ N ₅ OS ₃



286527: C22 H30 N4 O2 S2

SOURCE – AstraZeneca.

REFERENCES

1. Austin, R. et al. (Astra Pharmaceuticals, Ltd.; Astra AB) *Novel thiazolopyrimidine cpds.* WO 0009511.

WOUND-HEALING AGENTS

NAB2

285638

ACTION – Transcriptional repressor protein (NGFI-A binding corepressor) for use in wound healing and particularly in the downregulation of cell proliferative disorders associated with wound healing such as hypertrophic and keloid scar formation, psoriasis, restenosis following percutaneous transluminal coronary angioplasty, vessel wall calcification and cell proliferation in cancer, and preferably hypertrophic and keloid scar formation. Compound is reported to repress Egr-1 (early growth response gene)-mediated activation of growth factors, thereby slowing down the healing process and reducing scarring during healing. The use of poly-nucleotides encoding this protein for gene therapy applications is particularly preferred. In pharmacological studies, constructs expressing this protein were shown to block basal levels and Egr-1-mediated activation of growth factors such as PDGF-AB, TGF-β and VEGF in human vascular smooth muscle cells (HVSMC), as well as Egr-1-induced angiogenesis *in vitro*. When tested *in vivo* in a rat model of incisional wound healing, wounds transfected with this protein did not show impairment of the rate of healing; in addition, it was shown to increase levels of TGF-β3, known to have antiscarring properties, in the epidermis and granulation tissue, while decreasing the levels of TGF-β1, a known scarring agent, in the epidermis, and reduced the number of new blood vessels.

SOURCE – Glaxo Wellcome.

REFERENCES

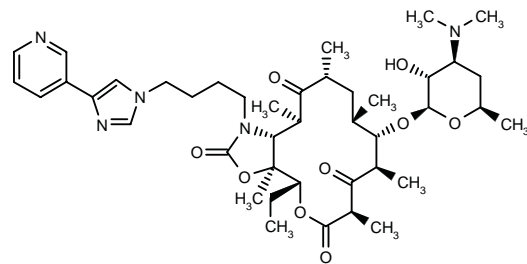
1. Braddock, M. and Campbell, C.J. (Glaxo Group Ltd.) *Pharmaceutical uses of NAB1 and NAB2.* WO 0003014.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

285673

6,11-Dideoxy-3-des(hexopyranosyloxy)-3-oxo-11-[N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]amino]erythromycin A 11-N,12-O-cyclic carbamate

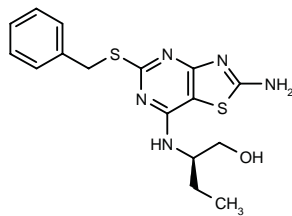


C42 H63 N5 O9; Mol wt: 781.9857

ANTIPSORIATICS

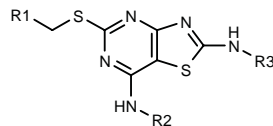
286526

2(R)-[2-Amino-5-(benzylsulfanyl)thiazolo[4,5-*d*]pyrimidin-7-ylamino]butan-1-ol

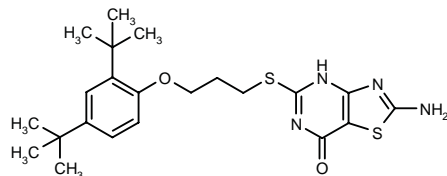


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286536	2,3-(F)2-Ph	4-imidazolyl-CH2CH2	H	C ₁₇ H ₁₅ F ₂ N ₇ S ₂
286540	Ph	C(Me)2CH2OH	(CH2)4Ph	C ₂₆ H ₃₁ N ₅ OS ₂
286542	Ph	C(Me)2CH2OH	CH(Ph)2	C ₂₉ H ₂₉ N ₅ OS ₂
286543	Ph	(CH2)5OH	4-imidazolyl-CH2CH2	C ₂₂ H ₂₇ N ₇ OS ₂
286544	Ph	CH2CH2OMe	2-thienyl-CH2CH2	C ₂₁ H ₂₃ N ₅ OS ₃



286527: C22 H30 N4 O2 S2

SOURCE – AstraZeneca.

REFERENCES

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WOUND-HEALING AGENTS

NAB2

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SOURCE – Glaxo Wellcome.

REFERENCES

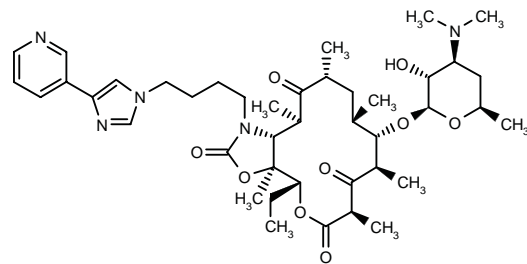
1. Braddock, M. and Campbell, C.J. (Glaxo Group Ltd.) *Pharmaceutical uses of NAB1 and NAB2.* WO 0003014.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

285673

6,11-Dideoxy-3-des(hexopyranosyloxy)-3-oxo-11-[N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]amino]erythromycin A 11-N,12-O-cyclic carbamate



C42 H63 N5 O9; Mol wt: 781.9857

ACTION – Ketolide antibiotic, an erythromycin derivative with potent activity against Gram-positive bacteria such as *Staphylococcus aureus* 011UC4 (MIC = 0.3 µg/ml), *Streptococcus agalactiae* 02B1SJ1c (MIC = 2.5 µg/ml), *Enterococcus faecalis* 02D2UC1 (MIC = 0.08 µg/ml), *Enterococcus faecium* 02D3HT1 (MIC = 0.04 µg/ml), *Streptococcus mitis* 02MitCB1 (MIC = 0.04 µg/ml) and *Streptococcus pneumoniae* 032UC1 (MIC = 0.02 µg/ml or less). Also reported to be active against *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia*, *Legionella*, *Ureaplasma*, *Toxoplasma* and *Mycobacterium*.

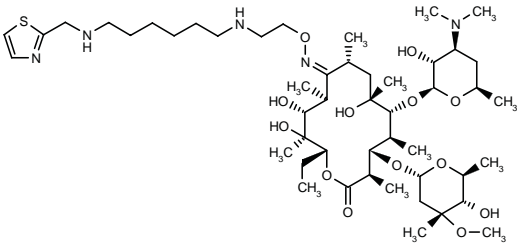
SOURCE – Aventis Pharma.

REFERENCES

1. Auger, J.-M. and Denis, A. (Aventis Pharma SA) *Novel 6-deoxy erythromycin derivs., method for preparing same and use as medicines*. FR 2781484, WO 0005239.

285800

Erythromycin A 9(E)-[O-[2-[6-(thiazol-2-ylmethylamino)-hexylamino]ethyl]oxime]



C49 H89 N5 O13 S; Mol wt: 988.3301

ACTION – Antibiotic, an erythromycin derivative with potent and broad-spectrum activity *in vitro* against Gram-positive and Gram-negative microorganisms such as *Streptococcus pneumoniae* (MIC = 0.0019-0.25 µg/ml), *Streptococcus group A* (MIC = 0.0078-0.5 µg/ml), *Streptococcus agalactiae* (MIC = 0.0078-0.25 µg/ml), *Staphylococcus aureus* (MIC = 0.25-1 µg/ml), *Haemophilus influenzae* (MIC = 1-8 µg/ml), *Branhamella catarrhalis* (MIC = 0.0019-0.125 µg/ml), *Klebsiella pneumoniae* (MIC = 16-32 µg/ml) and *Escherichia coli* (MIC = 1-8 µg/ml). When tested against clinically isolated erythromycin-resistant strains of *S. pneumoniae*, compound was clearly more potent than azithromycin (MIC = 0.25-4 µg/ml vs. 2-64 µg/ml for azithromycin). *In vivo*, it exhibits a longer duration of action than reference macrolides, efficacy persisting for up to 72 h postadministration. Thus, when tested in mice with experimental lung infection caused by *S. pneumoniae* UC41, it gave PD₅₀ values of 16.39 and 25.90 µmol/kg, respectively, when given orally at 24 and 48 h before infection versus PD₅₀ values of 16.45 and 34.13 µmol/kg, respectively, for azithromycin; in mice infected with *Streptococcus pyogenes* C203, it gave PD₅₀ values of 15.45, 16.39, 25.90 and 31.51 µmol/kg p.o., respectively, when administered 1 h after and 24, 48 or 72 h before infection versus PD₅₀ values of 5.32, 16.45, 34.13 and > 85.4 µmol/kg, respectively, for azithromycin.

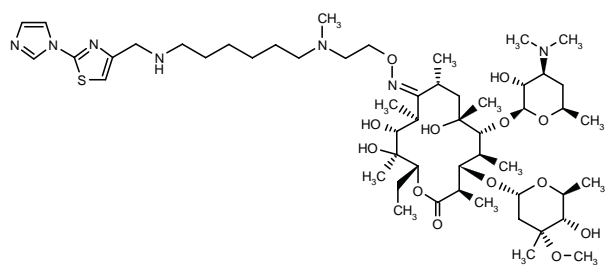
SOURCE – Zambon.

REFERENCES

1. Pellacini, F. et al. (Zambon Group SpA) *Erythromycin deriv. with antibiotic activity*. WO 0006586.

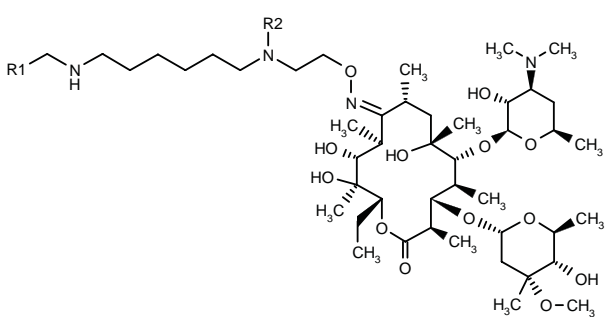
286225

Erythromycin A 9(E)-[O-[2-[N-[6-[2-(1H-imidazol-1-yl)-thiazol-4-ylmethylamino]hexyl]-N-methylamino]-ethyl]oxime]



C53 H93 N7 O13 S; Mol wt: 1068.4200

ACTION – Antibiotic, an erythromycin derivative with a broad spectrum of activity *in vitro* against Gram-positive and Gram-negative microorganisms, and superior activity compared to azithromycin against *Staphylococcus* spp. and *Streptococcus pneumoniae* with inducible resistance to erythromycin; it is further characterized by a good duration of action, showing prolonged therapeutic efficacy in lung infections, unlike clarithromycin. *In vitro*, compound gave MIC values of 2 and 4 µg/ml against *Staphylococcus epidermidis* 60 and *Staphylococcus* sp. 916 with inducible erythromycin resistance, and MIC values of 0.25-1 µg/ml against erythromycin-resistant *S. pneumoniae*. *In vivo*, compound was shown to be effective in mice with *Streptococcus pyogenes* C203-induced pulmonary infection when given either 1 h after or 24 h before infection (PD₅₀ = 10.1 and 16.0 µmol/kg p.o., respectively, vs. 7.38 and > 85.6 µmol/kg for clarithromycin). Other exemplified compounds from this series of erythromycin derivatives include the following:



Compound	R1	R2	Formula
286226	4-(2-thiazolyl)-2-thiazolyl	H	C ₅₂ H ₉₀ N ₆ O ₁₃ S ₂
286227	2-(4-Me-1,2,3-thiadiazol-5-yl)-4-thiazolyl	H	C ₅₂ H ₉₁ N ₇ O ₁₃ S ₂
286228	2-(2-thienyl)-4-thiazolyl	H	C ₅₃ H ₉₁ N ₅ O ₁₃ S ₂
286229	2-(1-pyrazolyl)-4-thiazolyl	Me	C ₅₃ H ₉₃ N ₇ O ₁₃ S

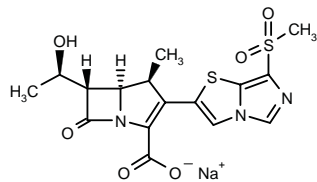
SOURCE – Zambon.

REFERENCES

1. Pellacini, F. et al. (Zambon Group SpA) *Erythromycin derivs. with antibiotic activity*. WO 0006606.

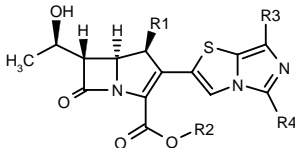
286291

(1*S*,5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[7-(methylsulfonyl)imidazo[5,1-*b*]thiazol-2-yl]carbapen-2-em-3-carboxylic acid sodium salt



C16 H16 N3 Na O6 S2; Mol wt: 433.4394

ACTION – Carbapenem antibiotic with potent *in vitro* activity against Gram-positive and Gram-negative bacteria including methicillin-resistant *Staphylococcus aureus* M126 (MIC = 1.56 µg/ml), *Staphylococcus epidermidis* ATCC14990 (MIC < 0.025 µg/ml), penicillin-resistant *Streptococcus pneumoniae* PRC9 (MIC = 0.05 µg/ml), *Haemophilus influenzae* PRC2 (MIC < 0.025 µg/ml), *Escherichia coli* NIHJ JC-2 (MIC = 0.05 µg/ml), *Klebsiella pneumoniae* PCI602 (MIC = 0.05 µg/ml) and β-lactamase-producing strains. It is stable to hydrolysis by porcine renal dehydropeptidase (DHP-I). LD₅₀ = 2000 mg/kg i.v. or higher in mice and rats. Other representative compounds within this series of carbapenem derivatives include the following:



Compound	R1	R2	R3	R4	Formula
286292	Me	Na	Ac	Me	C ₁₈ H ₁₈ N ₃ NaO ₅ S
286293	Me	Na	SOMe	H	C ₁₆ H ₁₆ N ₃ NaO ₅ S ₂
286294	H	Na	COEt	H	C ₁₇ H ₁₈ N ₃ NaO ₅ S
286295	Me	Na	SO ₂ Me	Me	C ₁₇ H ₁₈ N ₃ NaO ₆ S ₂
286296	Me	Na	COCH ₂ OH	H	C ₁₇ H ₁₆ N ₃ NaO ₆ S
286297	Me	Na	SO ₂ N(Me) ₂	H	C ₁₇ H ₁₉ N ₄ NaO ₆ S ₂
286298	Me	Na	SMe	H	C ₁₆ H ₁₆ N ₃ NaO ₄ S ₂
286522	Me	t-BuCOOCH ₂	SO ₂ Me	H	C ₂₂ H ₂₇ N ₃ O ₆ S ₂
286525	Me	2-Et-PhOCO ₂ CH(Me)	SMe	H	C ₂₇ H ₂₉ N ₃ O ₇ S ₂

SOURCE – Meiji Seika.

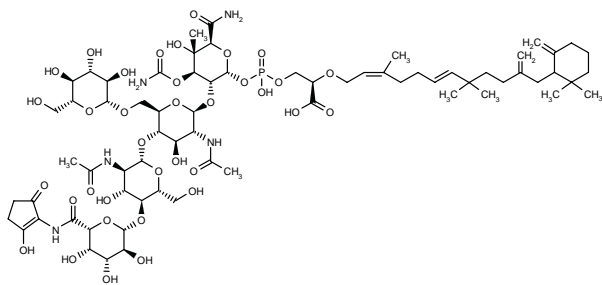
REFERENCES

1. Kano, Y. et al. (Meiji Seika Kaisha, Ltd.) *Novel carbapenem derivs.* WO 0006581.

AC-326-α

286020

3-[[*N*-(2-Hydroxy-5-oxo-1-cyclopenten-1-yl)-β-L-galactopyranuronamide]-(1→4)-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-[2-acetamido-2-deoxy-6-*O*-(β-D-glucopyranosyl)-β-D-glucopyranosyl]-(1→2)-(3-acetamido-3-deoxy-4-methyl-α-D-glucopyranuronamide-1-*O*-yl)]-(hydroxy)phosphoryloxy]-2(*R*)-[11-(2,2-dimethyl-6-methylenecyclohexylmethyl)-3,8,8-trimethyl-2(*Z*),6(*E*),11-dodecatrienyloxy]propionic acid



C69 H108 N5 O35 P; Mol wt: 1598.5860

ACTION – Phosphoglycolipid antibacterial agent extracted from the fermentation broth of an undefined *Actinomyces* species with potent antibacterial activity against Gram-positive organisms including *Staphylococcus aureus* (MIC < 0.06-0.25 µg/ml), *Staphylococcus haemolyticus* GC 4546 (MIC = 0.25 µg/ml), *Enterococcus faecalis* (including a vancomycin-resistant strain; MIC = 0.12-0.5 µg/ml), *Enterococcus faecium* (MIC < 0.06-0.25 µg/ml), *Streptococcus pyogenes* GC4563 (MIC = 0.25 µg/ml) and *Streptococcus pneumoniae* (MIC = 4-16 µg/ml). Compound showed poor activity against Gram-negative bacteria and *Candida albicans* (MIC > 64 µg/ml).

SOURCE – Wyeth-Ayerst.

REFERENCES

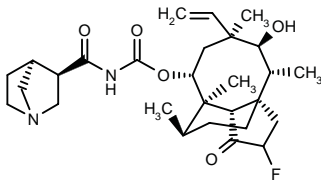
1. He, H. et al. *Isolation and structural elucidation of AC326-α, a new member of the moenomycin group.* J Antibiot 2000, 53(2): 191.

ANTIBACTERIAL DRUGS

286342

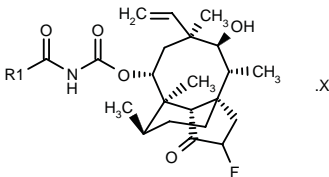
(3*R*,4*S*)-*N*-(1-Azabicyclo[2.2.1]hept-3-ylcarbonyl)-carbamic acid (1*S*,2*R*,3*S*,4*S*,6*R*,7*R*,8*S*,14*R*)-10-fluoro-3-hydroxy-2,4,7,14-tetramethyl-9-oxo-4-vinyltricyclo-[5.4.3.0^{1,8}]tetradec-6-yl ester

(3*R*,4*S*)-*N*-(1-Azabicyclo[2.2.1]hept-3-ylcarbonyl)-carbamic acid (3*aS*,4*R*,5*S*,6*S*,8*R*,9*R*,9*aS*,10*R*)-2-fluoro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-6-vinylperhydro-3*a*,9-propanocyclopentacyclooctan-8-yl ester



C28 H41 F N2 O5; Mol wt: 504.6389

ACTION – Antimicrobial mutilin derivative reported to be useful for the treatment of infections caused by Gram-positive and Gram-negative bacteria and *Mycoplasma* including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Haemophilus* spp., *Neisseria* spp., *Legionella* spp., *Chlamydia* spp., *Moraxella catarrhalis*, *Mycoplasma pneumoniae* and *Mycoplasma gallisepticum*. Other exemplified compounds are:



Compound	R1	X	Isomer	Formula
286343	(3 <i>R</i> ,4 <i>S</i>)-1-azabicyclo-[2.2.1]hept-3-yl	HCl	10 <i>S</i>	C ₂₈ H ₄₁ FN ₂ O ₅ .HCl
286344	4-MeO-Ph		10 <i>R</i>	C ₂₉ H ₃₈ FNO ₆
286345	4-MeO-Ph		10 <i>S</i>	C ₂₉ H ₃₈ FNO ₆

SOURCE – SmithKline Beecham.

REFERENCES

1. Brooks, G. and Hunt, E. (SmithKline Beecham plc) *2-Fluoro mutilin derivs.* WO 0007974.

SCRIP-5

285770

Secreted cysteine rich protein-5

ACTION – Cysteine-rich polypeptide from the scrp family of polypeptides that is believed to be structurally similar to the defensin family of antimicrobial and antifungal substances, and to growth factors and cytokines, and may therefore be of use in the treatment of cancer, inflammation, autoimmune diseases, allergy, asthma, rheumatoid arthritis, CNS inflammation, Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, amyotrophic lateral sclerosis, head injury and other neurological disorders, septic shock, stroke, osteoporosis, osteoarthritis, ischemia–reperfusion injury, cardiovascular, kidney and liver diseases, myocardial infarction, hypotension, hypertension, AIDS, myelodysplastic syndrome, aplastic anemia, male pattern baldness and bacterial, fungal, protozoal and viral infections. Also disclosed are polynucleotides encoding this polypeptide and methods for producing same by recombinant techniques.

SOURCE – SmithKline Beecham.

REFERENCES

1. Albone, E.F. and Kikly, K.K. (SmithKline Beecham Corp.) *Scrp-5: Secreted cysteine rich protein-5.* WO 0004923.

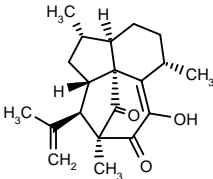
ANTIMYCOBACTERIAL AGENTS

ELISAPTEROSIN B

286210

(1*S*,5*S*,8*R*,9*S*,11*S*,12*S*,14*R*)-3-Hydroxy-1,5,9-trimethyl-14-(1-methylvinyl)tetracyclo[9.2.1.0^{4,12}.0^{8,12}]tetradec-3-ene-2,13-dione

(2*S*,2*aR*,5*S*,8*S*,9*R*,9*aS*,9*bS*)-6-Hydroxy-2,5,8-trimethyl-9-(1-methylethenyl)-1,2,2*a*,3,4,5,7,8,9,9*a*-decahydro-8,9*b*-methanobenz[*c,d*]azulene-7,10-dione



C20 H26 O3; Mol wt: 314.4224

Crystalline solid, [α]_D²⁵ –3.0° (c 4.4 CHCl3).

ACTION – Antimycobacterial agent extracted from the West Indian sea whip *Pseudopterogorgia elisabethae*, with strong activity against *Mycobacterium tuberculosis* (79% inhibition at 12.5 µg/ml); it did not exert significant cytotoxicity against CNS (SF-268), lung (NCI-H460) or breast (MCF-7) cancer cells.

SOURCES – Universidad de Puerto Rico, San Juan (PR); University of Missouri, Columbia, MO (US).

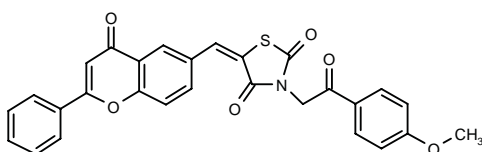
REFERENCES

1. Rodriguez, A.D. et al. Novel terpenoids from the West Indian Sea whip *Pseudopterorgia elisabethae* (Bayer). *Elisapterosins A and B: Rearranged diterpines possessing an unprecedented cage-like framework*. J Org Chem 2000, 65(5): 1390.

ANTIFUNGAL AGENTS

285997

3-[2-(4-Methoxyphenyl)-2-oxoethyl]-5-(4-oxo-2-phenyl-4H-1-benzopyran-6-ylmethylene)thiazolidine-2,4-dione



C28 H19 N O6 S; Mol wt: 497.5251

ACTION – Antimicrobial agent, a thiazolidinone derivative with comparable activity to fluconazole against *Candida albicans* (MIC = 12.5 µg/ml) and antibacterial activity against *Staphylococcus aureus* (MIC = 12.5 µg/ml), but inactive against *Escherichia coli*.

SOURCE – Ankara Üniversitesi, Ankara (TR).

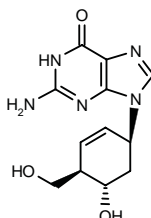
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1. Ayhan-Killergil, G. and Altanlar, N. *Synthesis of 3-substituted phenacyl-5-[2-phenyl-4H-4-oxo-1-benzopyran-6-yl(methylenyl)]thiazolidine-2,4-diones and evaluation of their antimicrobial activity*. Arzneim-Forsch Drug Res 2000, 50(2): 154.

ANTIVIRAL DRUGS

285836

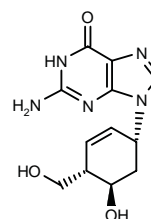
9-[5(S)-Hydroxy-4(R)-(hydroxymethyl)-2-cyclohexen-1(S)-yl]guanine



C12 H15 N5 O3; Mol wt: 277.2825

M.p. > 230 °C.

ACTION – Antiviral agent active against a wide range of herpesviruses including herpes simplex virus type 1 (HSV-1; IC₅₀ = 0.002-0.004 µg/ml) and type 2 (HSV-2; IC₅₀ = 0.05-0.07 µg/ml), varicella-zoster virus (VZV; IC₅₀ = 0.49-0.64 µg/ml) and cytomegalovirus (CMV; IC₅₀ = 0.6-0.8 µg/ml). In addition, compound retained good activity against tyrosine kinase-deficient strains of HSV-1 and VZV (IC₅₀ = 0.38 and 2.1-2.8 µg/ml, respectively), although the activity was reduced compared to against wild-type virus strains. The antiviral spectrum of compound is very similar to that of aciclovir and ganciclovir. No cytotoxicity was detected in several different cell lines (HeLa, Vero, E6SM and HEL cells), indicating selective antiviral activity. The L-enantiomer displays a similar profile:



285837: C12 H15 N5 O3

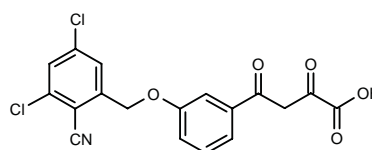
SOURCE – Rega Institute for Medical Research, Leuven (BE).

REFERENCES

1. Wang, J. et al. *The cyclohexene ring system as a furanose mimic: Synthesis and antiviral activity of both enantiomers of cyclohexenylguanine*. J Med Chem 2000, 43(4): 736.

286187

4-[3-(3,5-Dichloro-2-cyanobenzyloxy)phenyl]-2,4-dioxobutyric acid



C18 H11 Cl2 N O5; Mol wt: 392.1929

ACTION – Antiviral agent, a representative compound from a series of diketoacid derivatives with viral polymerase-inhibitory activity. Compound was shown to selectively inhibit hepatitis C virus NS5 RNA-dependent RNA polymerase (HCV Rd Rp) relative to other viral polymerases such as hepatitis B virus DNA-dependent RNA polymerase (HBV pol) and HIV reverse transcriptase, as demonstrated by an IC₅₀ value of 0.056 µM for HCV Rd Rp versus an IC₅₀ of 100 µM for HIV reverse transcriptase and no activity against HBV pol.

SOURCE – Istituto di Ricerche di Biologia Molecolare P. Angeletti.

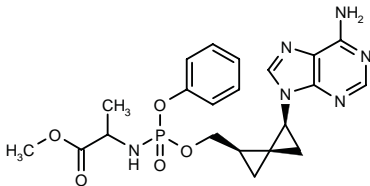
REFERENCES

1. Altamura, S. et al. (Istituto di Ricerche di Biologia Molecolare P. Angeletti SpA) *Diketoacid-derivs. as inhibitors of polymerases*. WO 0006529.

286209

2(*R,S*)-[[*(1R*,3S*,4S*)*-4-(6-Amino-9*H*-purin-9-yl)-spiro[2.2]pent-1-ylmethoxy](phenoxy)phosphorylamino]propionic acid methyl ester

N-[[*(1R*,3S*,4S*)*-4-(Adenin-9-yl)spiro[2.2]pent-1-ylmethoxy](phenoxy)phosphoryl]-*D,L*-alanine methyl ester



C21 H25 N6 O5 P; Mol wt: 472.4395

ACTION – Antiviral agent proven to inhibit human cytomegalovirus (HCMV) replication in human foreskin fibroblasts (EC_{50} = 0.38 μ M); it was also active against herpes simplex virus type 1 (HSV-1; EC_{50} = 7 and 20 μ M, respectively, in BSC-1 and Vero cells), HSV-2 (EC_{50} = 31 μ M in Vero cells), varicella-zoster virus (EC_{50} = 8.5 μ M in human foreskin fibroblasts), Epstein-Barr virus (EC_{50} = 2.8 μ M in Daudi cells), HIV-1 and hepatitis B virus (EC_{50} = 3.5 and 3.1 μ M in CEM-SS and 2.2.15 cells, respectively). Compound showed no cytotoxicity in human foreskin fibroblasts (IC_{50} = 100 μ M) and relatively low cytotoxic activity in BSC-1 and Vero cells (IC_{50} = 70 and 27 μ M, respectively), but it exhibited high cytotoxicity in Daudi cells (IC_{50} = 7.6 μ M). Compound is a substrate for pig liver esterase, indicating that the mechanism of its antiviral activity may be related to that of similar prodrugs of nucleoside analogues.

SOURCES – University of Alabama, Birmingham, AL (US); University of Michigan, Ann Arbor, MI (US); Wayne State University, Detroit, MI (US); Yale University, New Haven, CT (US).

REFERENCES

1. Guan, H.-P. et al. *Spiropentane mimics of nucleosides: Analogues of 2'-deoxyadenosine and 2'-deoxyguanosine. Synthesis of all stereoisomers, isomeric assignment, and biological activity.* J Org Chem 2000, 65(5): 1280.

AIDS MEDICINES

285861

AIDS vaccine containing at least one cytotoxic T-cell epitope of the Rev and/or Tat protein of HIV

ACTION – Immunogenic composition for preventing and treating HIV infection and progression to AIDS, designed based on the finding that the presence of cytotoxic T-cells to the Rev and/or Tat protein is indicative of a stable disease condition and favorable prognosis (lack of disease progression) in HIV-infected individuals. It acts by stimulating a cytotoxic T-cell response specific for the respective Rev and/or Tat protein in the host.

SOURCE – Erasmus University Rotterdam, Rotterdam (NL).

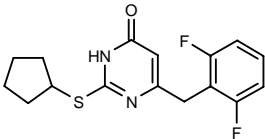
REFERENCES

1. van Baalen, C.A. and Osterhaus, A.D.M.E. (Erasmus University Rotterdam) *Induction of Rev and Tat specific cytotoxic T-cells for prevention and treatment of human immunodeficiency virus (HIV) infection.* US 6024965.

MC-867^{1,3}

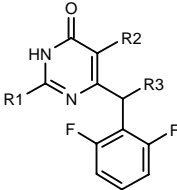
285541

2-(Cyclopentylsulfanyl)-6-(2,6-difluorobenzyl)pyrimidin-4(3*H*)-one



C16 H16 F2 N2 O S; Mol wt: 322.3774

ACTION – Antiviral agent for AIDS, an HIV reverse transcriptase inhibitor with potent anti-HIV-1 activity in infected MT-4 cells (IC_{50} = 0.08 μ M) and low cytotoxicity in uninfected cells (CC_{50} > 200 μ M; selectivity index > 2,500). Other exemplified compounds from this series of substituted 6-benzyl-4-oxopyrimidines include the following:



Compound	R1	R2	R3	Formula
MC-922 [285542] ^{1,3}	cyclopentyl-S	Me	H	C ₁₇ H ₁₈ F ₂ N ₂ OS
MC-1008 [285543] ^{1,3}	cyclopentyl-S	H	Me	C ₁₇ H ₁₈ F ₂ N ₂ OS
MC-1047 [285544] ^{1,3}	cyclopentyl-S	Me	Me	C ₁₈ H ₂₀ F ₂ N ₂ OS
MC-1161 [285545] ^{1,2}	SCH2SMe	H	H	C ₁₃ H ₁₂ F ₂ N ₂ OS ₂
MC-1162 [285546] ^{1,2}	SCH2SMe	Me	H	C ₁₄ H ₁₄ F ₂ N ₂ OS ₂
MC-1145 [285547] ^{1,2}	SCH2SMe	i-Pr	H	C ₁₆ H ₁₈ F ₂ N ₂ OS ₂
MC-1022 [285548] ¹	cyclopentyl-NH	H	H	C ₁₆ H ₁₇ F ₂ N ₃ O
MC-1050 [285549] ¹	cyclopentyl-NH	Me	H	C ₁₇ H ₁₉ F ₂ N ₃ O
MC-1048 [285550] ¹	cyclopentyl-NH	H	Me	C ₁₇ H ₁₉ F ₂ N ₃ O
MC-1129 [285551] ¹	cyclopentyl-NH	Me	Me	C ₁₈ H ₂₁ F ₂ N ₃ O
MC-1193 [285552] ¹	4-thiomorpholinyl	H	H	C ₁₅ H ₁₅ F ₂ N ₃ OS
MC-1182 [285553] ¹	N(Me)2	H	H	C ₁₃ H ₁₃ F ₂ N ₃ O

SOURCE – Novirio.

REFERENCES

1. La Colla, P. and Artico, M. (Novirio Pharmaceuticals Ltd.) *Substd. 6-benzyl-4-oxopyrimidines, process for their preparation and pharmaceutical compsns. containing them.* WO 0003998.

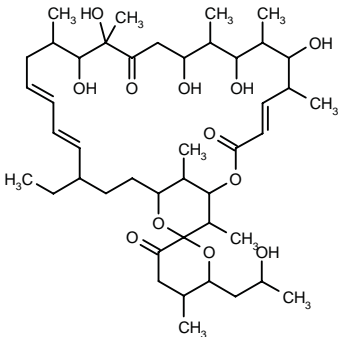
2. Marceddu, T. et al. *Does the 2-methylthiomethyl substituent really confer high anti-HIV-1 activity to S-DABOs?* Antivir Res 2000, 46(1): Abst 28.

3. Musiu, C. et al. *Sensitivity of mutant HIV-1 rRT to DABOs.* Antivir Res 2000, 46(1): Abst 44.

MER-5504A1

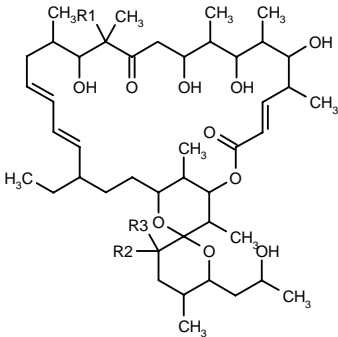
286110

22-Ethyl-7,9,11,14,15-pentahydroxy-6'-(2-hydroxypropyl)-5',6,8,10,14,16,28,29-octamethylspiro[2,26-dioxabicyclo[23.3.1]nonacosa-4(E),18(E),20(E)-triene-27,2'-tetrahydropyran]-3,3',13-trione



C44 H72 O12; Mol wt: 793.0408

ACTION – Antiviral agent for AIDS isolated from the microorganism *Streptomyces aburaviensis* Mer-5504 (FERM P-16648), proven to inhibit giant cell formation in HIV-infected MT-4 cells at a concentration of 10 ng/ml. Other compounds isolated from the same source are:



Compound	R1	R2	R3	Formula
Mer-5504A2 [286112]	OH	-O-		C ₄₅ H ₇₄ O ₁₂
Mer-5504A3 [286113]	OH	H	H	C ₄₅ H ₇₆ O ₁₁
Mer-5504A4 [286114]	H	H	H	C ₄₅ H ₇₆ O ₁₀

SOURCE – Mercian.

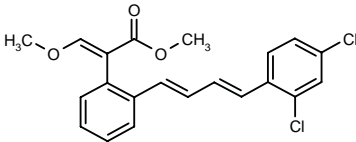
REFERENCES

1. Kawamura, N. et al. (Mercian Corp.) *HIV proliferation inhibitors and their preparation method*. JP 2000026468.

TREATMENT OF PROTOZOAL DISEASES

285814

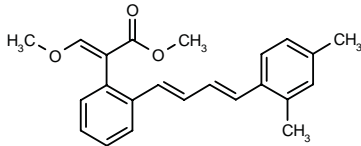
2-[2-[4-(2,4-Dichlorophenyl)-1(E),3(E)-butadienyl]phenyl]-3-methoxy-2(E)-propenoic acid methyl ester



C21 H18 Cl2 O3; Mol wt: 389.2762

M.p. 125-6 °C.

ACTION – Antimalarial agent active *in vitro* against chloroquine-sensitive (NF54) and chloroquine-resistant (K1) *Plasmodium falciparum* (IC₅₀ = 0.03 and 0.1 ng/ml, respectively). Compound exhibited good *in vivo* efficacy against *Plasmodium berghei* replication in infected mice (ED₅₀ = 1.07 and 0.33 mg/kg after s.c. and p.o. administration, respectively; ED₉₀ = 4.03 and 1.8 mg/kg, respectively); it was at least 2-fold more active than chloroquine but less active than atovaquone. Within this series of phenyl β-methoxyacrylates, the following is also included:



285815: C23 H24 O3

SOURCE – Roche.

REFERENCES

1. Alzeer, J. et al. (F. Hoffmann-La Roche AG) *β-Alkoxyacrylates against malaria*. EP 0996439, WO 9902150.
2. Alzeer, J. et al. *Phenyl β-methoxyacrylates: A new antimalarial pharmacophore*. J Med Chem 2000, 43(4): 560.

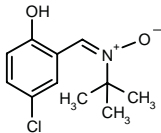
TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

285487

N-tert-Butyl-*N*-(5-chloro-2-hydroxybenzylidene)amine *N*-oxide

N-tert-Butyl-α-(5-chloro-2-hydroxyphenyl)nitron

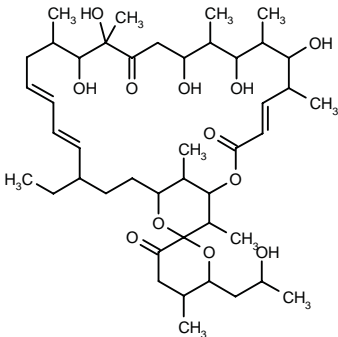


C11 H14 Cl N O2; Mol wt: 227.6896

MER-5504A1

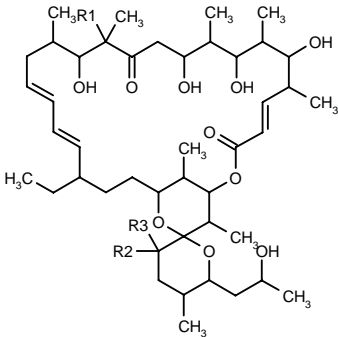
286110

22-Ethyl-7,9,11,14,15-pentahydroxy-6'-(2-hydroxypropyl)-5',6,8,10,14,16,28,29-octamethylspiro[2,26-dioxabicyclo[23.3.1]nonacosa-4(E),18(E),20(E)-triene-27,2'-tetrahydropyran]-3,3',13-trione



C44 H72 O12; Mol wt: 793.0408

ACTION – Antiviral agent for AIDS isolated from the microorganism *Streptomyces aburaviensis* Mer-5504 (FERM P-16648), proven to inhibit giant cell formation in HIV-infected MT-4 cells at a concentration of 10 ng/ml. Other compounds isolated from the same source are:



Compound	R1	R2	R3	Formula
Mer-5504A2 [286112]	OH	-O-		C ₄₅ H ₇₄ O ₁₂
Mer-5504A3 [286113]	OH	H	H	C ₄₅ H ₇₆ O ₁₁
Mer-5504A4 [286114]	H	H	H	C ₄₅ H ₇₆ O ₁₀

SOURCE – Mercian.

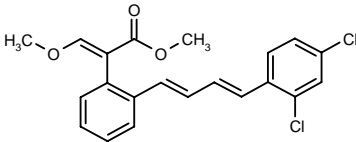
REFERENCES

1. Kawamura, N. et al. (Mercian Corp.) *HIV proliferation inhibitors and their preparation method*. JP 2000026468.

TREATMENT OF PROTOZOAL DISEASES

285814

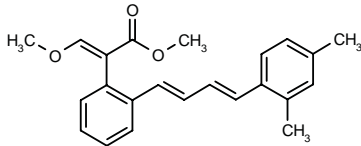
2-[2-[4-(2,4-Dichlorophenyl)-1(E),3(E)-butadienyl]phenyl]-3-methoxy-2(E)-propenoic acid methyl ester



C21 H18 Cl2 O3; Mol wt: 389.2762

M.p. 125-6 °C.

ACTION – Antimalarial agent active *in vitro* against chloroquine-sensitive (NF54) and chloroquine-resistant (K1) *Plasmodium falciparum* (IC₅₀ = 0.03 and 0.1 ng/ml, respectively). Compound exhibited good *in vivo* efficacy against *Plasmodium berghei* replication in infected mice (ED₅₀ = 1.07 and 0.33 mg/kg after s.c. and p.o. administration, respectively; ED₉₀ = 4.03 and 1.8 mg/kg, respectively); it was at least 2-fold more active than chloroquine but less active than atovaquone. Within this series of phenyl β-methoxyacrylates, the following is also included:



285815: C23 H24 O3

SOURCE – Roche.

REFERENCES

1. Alzeer, J. et al. (F. Hoffmann-La Roche AG) *β-Alkoxyacrylates against malaria*. EP 0996439, WO 9902150.
2. Alzeer, J. et al. *Phenyl β-methoxyacrylates: A new antimalarial pharmacophore*. J Med Chem 2000, 43(4): 560.

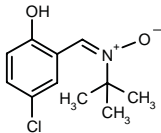
TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

285487

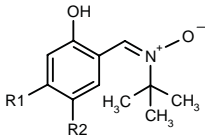
N-tert-Butyl-*N*-(5-chloro-2-hydroxybenzylidene)amine *N*-oxide

N-tert-Butyl-α-(5-chloro-2-hydroxyphenyl)nitron

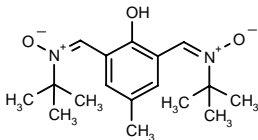


C11 H14 Cl N O2; Mol wt: 227.6896

ACTION – Antiinflammatory agent that is reported to act by inhibiting the production of cyclooxygenase type 2 (COX-2) but which does not inhibit COX-2 or COX-1 activity and is thus expected to exhibit fewer side effects as compared to direct inhibitors. Potentially useful in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, systemic lupus erythematosus, psoriatic arthritis, inflammatory bowel disease, septic shock, erythema nodosum leprosum, septicemia, uveitis and adult respiratory distress syndrome (ARDS). Other specifically claimed compounds from this series of α -(2-hydroxyphenyl)nitron derivatives include the following:



Compound	R1	R2	Formula
285489	H	NO2	C ₁₁ H ₁₄ N ₂ O ₄
285490	N(Et)2	H	C ₁₅ H ₂₄ N ₂ O ₂
285491	H	OCF3	C ₁₂ H ₁₄ F ₃ NO ₃



285488: C17 H26 N2 O3

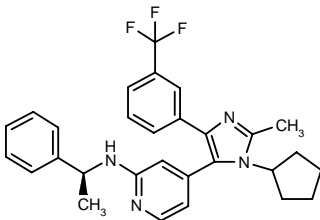
SOURCE – Centaur.

REFERENCES

1. Waterbury, L.D. et al. (Centaur Pharmaceuticals, Inc.) α -(2-Hydroxyphenyl) nitron cpds., pharmaceutical compsns. containing the same and their use for treating inflammation. WO 0003977.

285802

N-[4-[1-Cyclopentyl-2-methyl-4-[3-(trifluoromethyl)-phenyl]-1*H*-imidazol-5-yl]pyridin-2-yl]-*N*-[1(*S*)-phenylethyl]amine



C29 H29 F3 N4; Mol wt: 490.5701

ACTION – An inhibitor of the production or activity of cytokines such as IL-1, IL-6, IL-8 and TNF- α with potential in the treatment of cytokine-mediated diseases such as rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, atherosclerosis, cachexia, septic shock, adult respiratory distress syndrome and osteoporosis. A specifically claimed compound from a series of substituted imidazole derivatives.

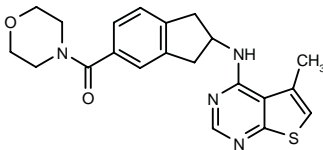
SOURCE – Merck & Co.

REFERENCES

1. Claiborne, C.F. et al. (Merck & Co., Inc.) *Substd. imidazoles having cytokine inhibitory activity*. WO 0006563.

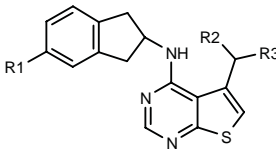
285991

1-[2-(5-Methylthieno[2,3-*d*]pyrimidin-4-ylamino)indan-5-yl]-1-(4-morpholinyl)methanone



C21 H22 N4 O2 S; Mol wt: 394.4968

ACTION – NF- κ B inhibitor whose activity was demonstrated *in vitro* by inhibition of human inducible nitric oxide synthase (iNOS) gene expression stimulated by IL-1 β + TNF- α in transfected human lung cancer A549-derived cells (IC₅₀ = 0.051 μ M), as well as by inhibition of NF- κ B activity in transfected A549 cells stimulated by IL-1 β or TNF- α (IC₅₀ = 0.051 and 0.089 μ M, respectively). In addition, it was shown to inhibit lipopolysaccharide-stimulated NO and TNF- α production in murine macrophage-derived RAW264.7 cells with IC₅₀ values of 0.025 and 0.051 μ M, respectively. *In vivo*, it inhibited carrageenan-induced paw edema formation in rats at a dose of 1.0 mg/kg i.p. A representative compound from a series of indane derivatives, wherein the following are also included:



Compound	R1	R2=R3	Formula
285992	H	H	C ₁₆ H ₁₅ N ₃ S
285993	H	Me	C ₁₈ H ₁₉ N ₃ S
285994	CONHCH2Ph	H	C ₂₄ H ₂₂ N ₄ OS

SOURCE – Suntory.

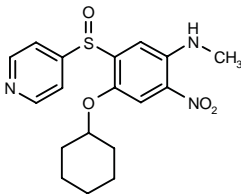
REFERENCES

1. Nunokawa, Y. et al. (Suntory Ltd.) *NF κ B inhibitors containing indan derivs. as the active ingredient*. WO 0005234.

286057¹

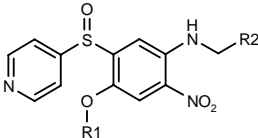
N-[4-(Cyclohexyloxy)-2-nitro-5-(4-pyridinylsulfinyl)phenyl]-*N*-methylamine

4-(Cyclohexyloxy)-2-nitro-5-(4-pyridylsulfinyl)-*N*-methyl-aniline



C18 H21 N3 O4 S; Mol wt: 375.4469

ACTION – Agent for the treatment of inflammatory disorders and autoimmune diseases such as chronic rheumatoid arthritis, bone diseases such as osteoporosis and allergy that acts by inhibiting the production of inflammatory cytokines. *In vitro*, compound was shown to inhibit concanavalin A (ConA)-stimulated IL-5 production in murine spleen cells and human peripheral blood mononuclear cells (PBMCs) with IC₅₀ values of 6.7 and 2.9 µM, respectively; in addition, it was found to inhibit ConA-stimulated IL-1β and IL-6 production in PBMCs by 35-95% and 80-95% at 0.3 µg/ml, respectively. Other compounds from this series of *N*-substituted nitroaniline derivatives include the following:



Compound	R1	R2	Formula
286058 ^{1,2}	Me	H	C ₁₃ H ₁₃ N ₃ O ₄ S
286059 ¹	Me	Ph	C ₁₉ H ₁₇ N ₃ O ₄ S
286060 ¹	C6H13	H	C ₁₈ H ₂₃ N ₃ O ₄ S
286061 ¹	cyclohexyl	CO2Me	C ₂₀ H ₂₃ N ₃ O ₆ S

SOURCE – Taisho.

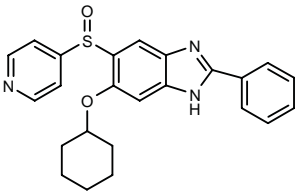
REFERENCES

1. Saito, S. et al. (Taisho Pharmaceutical Co., Ltd.) *N*-Substd. nitroaniline derivs. JP 2000007626.

2. Saito, H. et al. *Synthesis of novel sulfoxide derivatives having cytokine production inhibitory activity (1)*. 120th Annu Meet Pharm Soc Jpn (March 29-31, Gifu) 2000, Abst 30-PB-12-11.

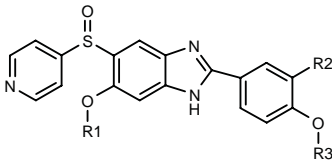
286129

6-(Cyclohexyloxy)-2-phenyl-5-(4-pyridylsulfinyl)-1*H*-benzimidazole



C24 H23 N3 O2 S; Mol wt: 417.5307

ACTION – Agent for the treatment of inflammatory, autoimmune and bone disorders and allergies, an inhibitor of the production of inflammatory cytokines. *In vitro*, compound inhibited concanavalin A (ConA)-stimulated production of IL-5 in murine spleen cells (76% inhibition at 0.3 µg/ml), as well as ConA-stimulated IL-1β and IL-6 production in human peripheral blood monocytes (36-64% and 55-93% inhibition, respectively, at 0.3 µg/ml). Other compounds from this series of 2,5,6-substituted benzimidazole derivatives include the following:



Compound	R1	R2	R3	Formula
286130	Me	H	Me	C ₂₀ H ₁₇ N ₃ O ₃ S
286131	Me	H	H	C ₁₉ H ₁₅ N ₃ O ₃ S
286132	cyclohexyl	cyclopentyl-O	Me	C ₃₀ H ₃₃ N ₃ O ₄ S

SOURCE – Taisho.

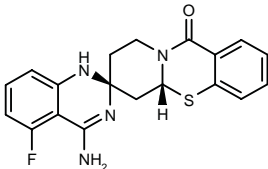
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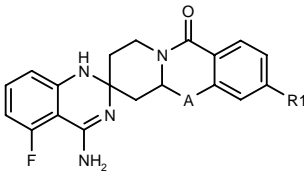
286146

(5*aR**,7*R**)-4'-Amino-5'-fluoro-1',2',6,7,8,9-hexahydro-5*aH*,11*H*-spiro[pyrido[2,1-*b*][1,3]benzothiazine-7,2'-quinazolin]-11-one



C19 H17 F N4 O S; Mol wt: 368.4343

ACTION – Agent for the treatment of inflammatory disorders and pain, an inhibitor of inducible nitric oxide synthase (iNOS). Other specifically claimed compounds within this series of aminospiriperidine quinazoline derivatives include the following:



Compound	R1	A	Isomer	Formula
286147	H	S	5 <i>aR</i> *,7 <i>S</i> *	C ₁₉ H ₁₇ FN ₄ OS
286148	H	O	5 <i>aR</i> *,7 <i>R</i> *	C ₁₉ H ₁₇ FN ₄ O ₂
286149	H	O	5 <i>aR</i> *,7 <i>S</i> *	C ₁₉ H ₁₇ FN ₄ O ₂
286150	Cl	O	5 <i>aR</i> *,7 <i>R</i> *	C ₁₉ H ₁₆ ClFN ₄ O ₂
286151	Cl	O	5 <i>aR</i> *,7 <i>S</i> *	C ₁₉ H ₁₆ ClFN ₄ O ₂

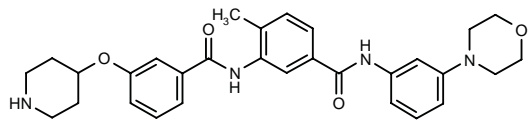
SOURCE – AstraZeneca.

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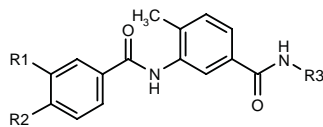
286368

4-Methyl-*N*-[3-(4-morpholinyl)phenyl]-3-[3-(4-piperidinylidinyloxy)benzamido]benzamide



C30 H34 N4 O4; Mol wt: 514.6226

ACTION – An inhibitor of the production of cytokines such as TNF- α and various interleukins such as IL-1, IL-6 and IL-8, with potential in the treatment of cytokine-mediated disorders such as rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischemic heart disease and psoriasis. Compound was shown to inhibit p38 α kinase activity with an IC₅₀ of about 0.05 μ M and lipopolysaccharide-stimulated TNF- α production in human whole blood with an IC₅₀ of approximately 2 μ M. A representative compound from a series of amide derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
286371	OMe	H	3-N(Me)2-Ph	C ₂₄ H ₂₅ N ₃ O ₃
286372	OMe	OMe	cyclohexyl-CH ₂ CH ₂	C ₂₅ H ₃₂ N ₂ O ₄
286373	-CH=CHCH=N-		3-N(Me)2-Ph	C ₂₆ H ₂₄ N ₄ O ₂
286374	4-Me-1-Piz-CH ₂	H	3-(4-morpholinyl)-Ph	C ₃₁ H ₃₇ N ₅ O ₃
286375	H	CH ₂ N(Et)2	3-(4-morpholinyl)-Ph	C ₃₀ H ₃₆ N ₄ O ₃

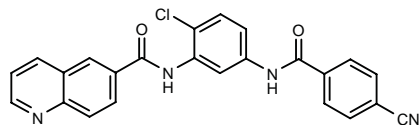
SOURCE – AstraZeneca.

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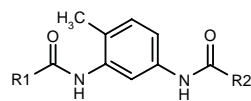
286409

N-[2-Chloro-5-(4-cyanobenzamido)phenyl]quinoline-6-carboxamide



C24 H15 Cl N4 O2; Mol wt: 426.8615

ACTION – An inhibitor of the production of cytokines such as TNF- α , IL-1, IL-6 and IL-8 that acts by inhibiting p38 kinase activity. *In vitro*, compound had an IC₅₀ value of about 0.05 μ M against human recombinant p38 α and inhibited TNF- α production in human peripheral blood mononuclear cells stimulated with lipopolysaccharide with an IC₅₀ of about 2 μ M. Potentially useful in the treatment of cytokine-mediated disorders such as rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischemic heart disease and psoriasis. Other compounds within this series of amide derivatives include the following:



Compound	R1	R2	Formula
286410	6-Cl-3-Pyr	3-N(Me)2-Ph	C ₂₂ H ₂₁ ClN ₄ O ₂
286411	6-benzothieryl	3-N(Me)2-Ph	C ₂₅ H ₂₃ N ₃ O ₂ S
286412	6-quinolyl	5-isoxazolyl	C ₂₁ H ₁₆ N ₄ O ₃
286413	6-[N(Me)2(CH ₂)3NH]-3-Pyr	2-(4-morpholinyl)-4-Pyr	C ₂₈ H ₃₆ N ₇ O ₃
286414	6-(1-Me-2-pyrrolidinyl-CH ₂ CH ₂ NH)-3-Pyr	2-(4-morpholinyl)-4-Pyr	C ₃₀ H ₃₇ N ₇ O ₃

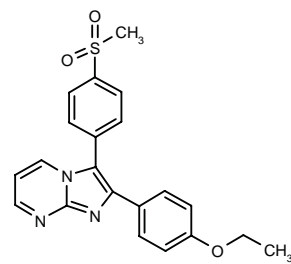
SOURCE – AstraZeneca.

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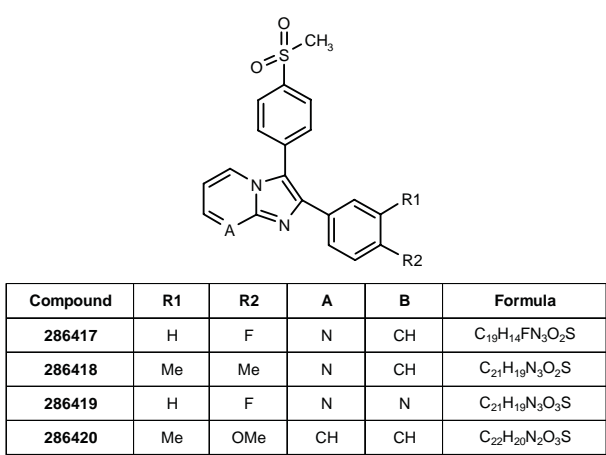
286416

2-(4-Ethoxyphenyl)-3-[4-(methylsulfonyl)phenyl]imidazo[1,2-*a*]pyrimidine



C21 H19 N3 O3 S; Mol wt: 393.4651

ACTION – Antiinflammatory agent, a selective cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 1.0 and 50 μ M for inhibition of COX-2 and COX-1, respectively, in human whole blood). Other specifically claimed compounds within this series of substituted imidazo[1,2-*a*]azines include the following:



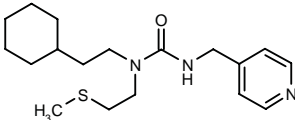
SOURCE – Salvat.

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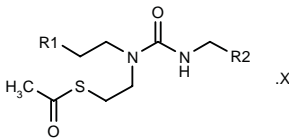
286612

N¹-(2-Cyclohexylethyl)-N¹-[2-(methylsulfanyl)ethyl]-N³-(4-pyridylmethyl)urea



C18 H29 N3 O S; Mol wt: 335.5131

ACTION – Agent for the treatment of autoimmune diseases such as rheumatoid arthritis that acts by inhibiting the production of TNF-α, as demonstrated *in vivo* in lipopolysaccharide-treated rats (81.2% inhibition at 10 mg/kg p.o.). Other compounds from this series of urea derivatives include the following:



Compound	R1	R2	X	Formula
286613	cyclohexyl	4-Pyr-CH2CH2		C ₂₁ H ₃₃ N ₃ O ₂ S
286614	Ph	3-Pyr-CH2CH2		C ₂₁ H ₂₇ N ₃ O ₂ S
286615	cyclohexyl	4-Pyr	HCl	C ₁₉ H ₂₉ N ₃ O ₂ S.HCl
286616	cyclopentyl	4-Pyr	HCl	C ₁₈ H ₂₇ N ₃ O ₂ S.HCl
286617	1-adamantyl	4-Pyr	HCl	C ₂₃ H ₃₃ N ₃ O ₂ S.HCl

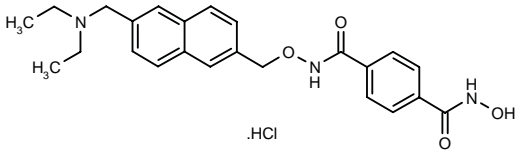
SOURCE – Santen.

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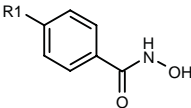
286687

4-[N-[6-(Diethylaminomethyl)-2-naphthylmethoxy]-carbamoyl]benzohydroxamic acid hydrochloride



C24 H27 N3 O4 . HCl; Mol wt: 457.9552

ACTION – Antiinflammatory and immunosuppressive agent shown to inhibit lipopolysaccharide (LPS)-stimulated production of IL-1β in human peripheral blood mononuclear cells (PBMCs; IC₅₀ = 96 nM) and LPS-stimulated TNF-α release in mice (55.0 and 64.3% inhibition, respectively, at 0.5 and 5.0 mg/kg p.o.). Other specifically claimed compounds from this series of hydroxamic acid derivatives include the following:



Compound	R1	Formula
286688	NHCO(CH2)4Ph	C ₁₈ H ₂₀ N ₂ O ₃
286689	CH2CONHOCH2CH(Ph)2	C ₂₃ H ₂₂ N ₂ O ₄
286690	CONHOCH2CH2CH(Ph)2	C ₂₃ H ₂₂ N ₂ O ₄
286691	1-adamantyl-CH2CH2ONHCO	C ₂₀ H ₂₆ N ₂ O ₄
286692	1-Naph-CH2ONHCO	C ₁₉ H ₁₆ N ₂ O ₄
286693	2-Naph-CH2ONHCO	C ₁₉ H ₁₆ N ₂ O ₄
286694	1,2,3,4-tetrahydro-2-Naph-CH2ONHCO	C ₁₉ H ₂₀ N ₂ O ₄
286695	CONHO(CH2)3Ph	C ₁₇ H ₁₈ N ₂ O ₄
286696	(E)-CONHCH2CH=CHPh	C ₁₇ H ₁₆ N ₂ O ₃
286698	6-[N(Pr)2CH2]-2-Naph-CH2ONHCO	C ₂₆ H ₃₁ N ₃ O ₄
286699	6-[N(Bu)2CH2]-2-Naph-CH2ONHCO	C ₂₈ H ₃₅ N ₃ O ₄
286701	4-[N(Et)2CH2]-1-Naph-CH2ONHCO	C ₂₄ H ₂₇ N ₃ O ₄
286702	6-[N(Et)2CH2]-2-Naph-CH2NHNHCO	C ₂₄ H ₂₈ N ₄ O ₃
286704	2-i-Pr-1,2,3,4-tetrahydro-3-isoquinolinyl-CH2ONHCOCH2	C ₂₂ H ₂₇ N ₃ O ₄

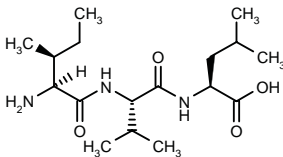
SOURCE – Italfarmaco.

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286747

L-Isoleucyl-L-valyl-L-leucine



C17 H33 N3 O4; Mol wt: 343.4647

ACTION – Antiinflammatory peptide derived from the enzymatic degradation of IL-2 by neutrophil elastase, with potential in the treatment of inflammatory and autoimmune disorders, particularly rheumatoid arthritis, diabetes type I, multiple sclerosis, systemic lupus erythematosus, uveitis and inflammatory bowel disease. Compound was shown to inhibit IL-2- and MIP-1 β -induced chemotaxis of human T-cells through fibronectin-coated polycarbonate membranes at picomolar concentrations and also inhibited T-cell adhesion to fibronectin, laminin and collagen type IV induced by various stimuli. In addition, compound was shown to completely inhibit spontaneous IL-8 secretion from HT-29 cells at 1 nM and is also reported to inhibit TNF- α -induced secretion of IL-1 β from HT-29 or Caco-2 cells.

SOURCE – Yeda.

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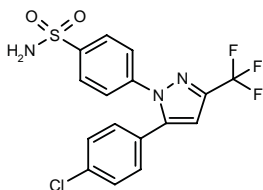
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SC-58236*

226722

4-[5-(4-Chlorophenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide

SC-236



C16 H11 Cl F3 N3 O2 S; Mol wt: 401.7970

M.p. 143-5 °C.

ACTION – Potent and selective cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 0.01 and 17.8 μ M against COX-2 and COX-1, respectively) with oral antiinflammatory activity in acute and chronic rat models of inflammation (ED₅₀ = 5.4 and 0.07 mg/kg, respectively, in the carrageenan-induced paw edema and adjuvant-induced arthritis assays). Compound also showed analgesic activity in the carrageenan-induced hyperalgesia test in rats (ED₅₀ = 6.6 mg/kg). In an *in vitro* model of *in vivo* allergic events, compound was shown to modulate histamine release from blood basophils from allergic patients, suggesting a role for selective COX-2 inhibitors as modulators of the late-phase allergic response where basophils play a critical role. Potentially useful for the treatment of acute and chronic inflammatory diseases including rheumatoid arthritis and osteoarthritis.

SOURCE – Pharmacia.

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*Identified compound **226722** Drug Data Rep 1995, 017(11): 1039.

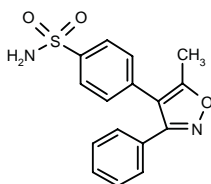
VALDECOXIB*

Prop INN; USAN

241522

4-(5-Methyl-3-phenylisoxazol-4-yl)benzenesulfonamide

SC-65872



C16 H14 N2 O3 S; Mol wt: 314.3660

ACTION – Antiinflammatory agent, a potent and selective inhibitor of cyclooxygenase type 2 (COX-2; IC₅₀ = 0.005 μM against human recombinant enzyme) as compared to COX-1 (IC₅₀ = 140 μM). In human whole blood, it was able to inhibit lipopolysaccharide-induced PGE₂ release (IC₅₀ = 0.89 μM) and, to a lesser extent, TxB₂ formation (IC₅₀ = 25.4 μM). In acute and chronic inflammation models in rats, compound exhibited potent oral activity, with respective ED₅₀ values of 10.2 and 0.032 mg/kg against carrageenan-induced edema and adjuvant-induced arthritis. In addition, it blocked prostaglandin production in the rat carrageenan air pouch model (ED₅₀ = 0.05 mg/kg p.o.). The active metabolite of compound, identified in rodents and dogs and also present at lower levels in humans, is also a selective COX-2 inhibitor (IC₅₀ = 0.18 and 1120 μM against COX-2 and COX-1, respectively). Currently in phase III clinical evaluation for the treatment of arthritis and pain.

SOURCES – Pfizer; Pharmacia; Yamanouchi.

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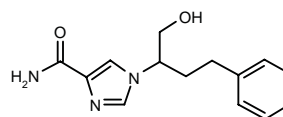
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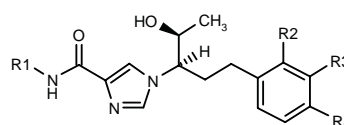
IMMUNOMODULATING AGENTS**285790**

1-[1-(Hydroxymethyl)-3-phenylpropyl]-1H-imidazole-4-carboxamide

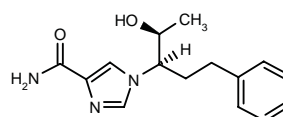


C14 H17 N3 O2; Mol wt: 259.3073

ACTION – Adenosine deaminase inhibitor (K_i = 5.9 μM) with potential in the treatment or prevention of auto-immune diseases, inflammatory conditions, organ or tissue transplant rejection, leukemia and conditions arising from or aggravated by insufficient blood flow. *In vivo*, compound was shown to reduce TNF-α levels and to increase IL-10 levels in lipopolysaccharide-treated mice. Other specifically claimed compounds from this series of imidazole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
285792	H	OCH2Ph	H	H	C ₂₂ H ₂₅ N ₃ O ₃
285793	H	-CH=CHCH=CH-		H	C ₁₉ H ₂₁ N ₃ O ₂
285794	H	OC6H13	H	H	C ₂₁ H ₃₁ N ₃ O ₃
285795	H	H	-CH=CHCH=CH-		C ₁₉ H ₂₁ N ₃ O ₂
285796	H	Cl	H	H	C ₁₅ H ₁₈ ClN ₃ O ₂
285797	H	Cl	Cl	H	C ₁₅ H ₁₇ Cl ₂ N ₃ O ₂
285798	C(=NH)NH2	-CH=CHCH=CH-		H	C ₂₀ H ₂₃ N ₃ O ₂
285799	H	O(CH2)3Ph	H	H	C ₂₄ H ₂₉ N ₃ O ₃

**285791:** C15 H19 N3 O2**SOURCE** – Fujisawa.

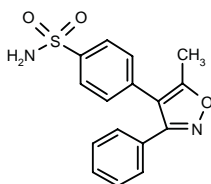
VALDECOXIB*

Prop INN; USAN

241522

4-(5-Methyl-3-phenylisoxazol-4-yl)benzenesulfonamide

SC-65872



C16 H14 N2 O3 S; Mol wt: 314.3660

ACTION – Antiinflammatory agent, a potent and selective inhibitor of cyclooxygenase type 2 (COX-2; IC₅₀ = 0.005 μM against human recombinant enzyme) as compared to COX-1 (IC₅₀ = 140 μM). In human whole blood, it was able to inhibit lipopolysaccharide-induced PGE₂ release (IC₅₀ = 0.89 μM) and, to a lesser extent, TxB₂ formation (IC₅₀ = 25.4 μM). In acute and chronic inflammation models in rats, compound exhibited potent oral activity, with respective ED₅₀ values of 10.2 and 0.032 mg/kg against carrageenan-induced edema and adjuvant-induced arthritis. In addition, it blocked prostaglandin production in the rat carrageenan air pouch model (ED₅₀ = 0.05 mg/kg p.o.). The active metabolite of compound, identified in rodents and dogs and also present at lower levels in humans, is also a selective COX-2 inhibitor (IC₅₀ = 0.18 and 1120 μM against COX-2 and COX-1, respectively). Currently in phase III clinical evaluation for the treatment of arthritis and pain.

SOURCES – Pfizer; Pharmacia; Yamanouchi.**REFERENCES**

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- Gregory, S.A. et al. (G.D. Searle & Co.) *Combinations having immunosuppressive effects, containing cyclooxygenase-2-inhibitors and 5-lipoxygenase inhibitors*. EP 0888127, WO 9729776.
- Gregory, S.A. et al. (G.D. Searle & Co.) *Compsns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B₄ receptor antagonist*. EP 0880362, WO 9729775.
- Isakson, P.C. et al. (G.D. Searle & Co.) *Combination of a cyclooxygenase-2 inhibitor and a leukotriene B₄ receptor antagonist for the treatment of inflammations*. JP 1999507669, WO 9641645.
- Isakson, P.C. et al. (G.D. Searle & Co.) *Compsns. comprising a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor*. JP 1999507670, WO 9641626.
- Isakson, P.C. et al. (G.D. Searle & Co.) *Compsns. comprising a cyclooxygenase-2 inhibitor and a leukotriene A₄ hydrolase inhibitor*. JP 1999507925, WO 9641625.
- Needleman, P. and Masferrer, J. (G.D. Searle & Co.) *Method of using cyclooxygenase-2 inhibitors in maintaining the fetal ductus arteriosus during treatment and prevention of preterm labor*. WO 9922720.
- Roniker, B. et al. (G.D. Searle & Co.) *Method of using cyclooxygenase-2 inhibitors in the prevention of cardiovascular disorders*. WO 9847509.
- Seibert, K. et al. (G.D. Searle & Co.) *Method of using cyclooxygenase-2 inhibitors in the treatment and prevention of neoplasia*. WO 9816227.
- Talley, J.J. (G.D. Searle & Co.) *Isoxazole cpds. as cyclooxygenase inhibitors*. US 5859257.
- Talley, J.J. et al. (G.D. Searle & Co.) *Crystalline form of 4-[5-methyl-3-phenylisoxazole-4-yl]benzenesulfonamide*. EP 0920422, WO 9806708.
- Talley, J.J. et al. (G.D. Searle & Co.) *Substd. isoxazoles for the treatment of inflammation*. EP 0809636, JP 1999503722, US 5633272, WO 9625405.

13. Talley, J.J. et al. (G.D. Searle & Co.) *Substd. sulfonylphenylheterocycles as cyclooxygenase-2 and 5-lipoxygenase inhibitors*. EP 0828736, EP 0995747, US 5643933, WO 9638442.

14. Talley, J.J. et al. *4-[5-Methyl-3-phenylisoxazol]4-yl]-benzenesulfonamide, valdecoxib: A potent and selective inhibitor of COX-2*. J Med Chem 2000, 43(5): 775.

15. *Monsanto: Q4 and year-end 1998 highlights*. DailyDrugNews.com (Daily Essentials) 1999, Jan 25.

16. *Pfizer: Q4 1998 highlights*. DailyDrugNews.com (Daily Essentials) 1999, Feb 19.

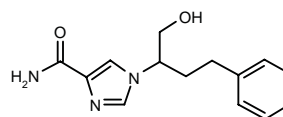
17. *Proposed international nonproprietary names (Prop. INN): List 80*. WHO Drug Inf 1998, 12(4): 282.

18. *Yamanouchi exercises option to license three Searle compounds*. DailyDrugNews.com (Daily Essentials) 2000, March 9.

*Identified compound **241522** (see **241000**) Drug Data Rep 1997, 019(01): 0074.

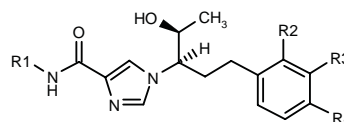
IMMUNOMODULATING AGENTS**285790**

1-[1-(Hydroxymethyl)-3-phenylpropyl]-1H-imidazole-4-carboxamide

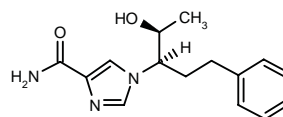


C14 H17 N3 O2; Mol wt: 259.3073

ACTION – Adenosine deaminase inhibitor (K_i = 5.9 μM) with potential in the treatment or prevention of auto-immune diseases, inflammatory conditions, organ or tissue transplant rejection, leukemia and conditions arising from or aggravated by insufficient blood flow. *In vivo*, compound was shown to reduce TNF-α levels and to increase IL-10 levels in lipopolysaccharide-treated mice. Other specifically claimed compounds from this series of imidazole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
285792	H	OCH2Ph	H	H	C ₂₂ H ₂₅ N ₃ O ₃
285793	H	-CH=CHCH=CH-		H	C ₁₉ H ₂₁ N ₃ O ₂
285794	H	OC6H13	H	H	C ₂₁ H ₃₁ N ₃ O ₃
285795	H	H	-CH=CHCH=CH-		C ₁₉ H ₂₁ N ₃ O ₂
285796	H	Cl	H	H	C ₁₅ H ₁₈ ClN ₃ O ₂
285797	H	Cl	Cl	H	C ₁₅ H ₁₇ Cl ₂ N ₃ O ₂
285798	C(=NH)NH2	-CH=CHCH=CH-		H	C ₂₀ H ₂₃ N ₃ O ₂
285799	H	O(CH2)3Ph	H	H	C ₂₄ H ₂₉ N ₃ O ₃

**285791:** C15 H19 N3 O2**SOURCE** – Fujisawa.

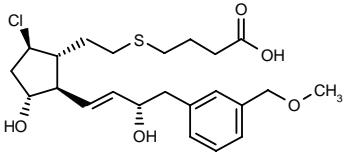
REFERENCES

1. Terasaka, T. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Imidazole cpds. and their use as adenosine deaminase inhibitors*. WO 0005217.

286044

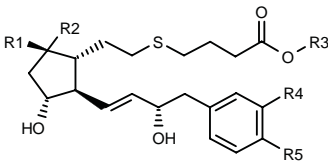
4-[2-[5(*R*)-Chloro-3(*R*)-hydroxy-2(*R*)-[3(*S*)-hydroxy-4-[3-(methoxymethyl)phenyl]-1(*E*)-butenyl]cyclopent-1(*R*)-yl]-ethylsulfanyl]butyric acid

9-Chloro-9-deoxy-16-[3-(methoxymethyl)phenyl]-5-thia-17,18,19,20-tetranorprostaglandin F_{1β}

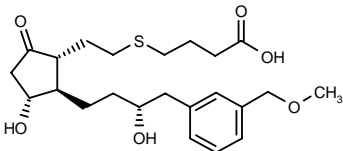


C23 H33 Cl O5 S; Mol wt: 457.0277

ACTION – Prostaglandin E derivative with potent and selective affinity for EP₄ receptors relative to other PGE₂ receptor subtypes, as demonstrated in binding assays by K_i values of > 10, > 10 and 0.0079 μM, respectively, for murine EP₁, EP_{3α} and EP₄ receptors cloned in CHO cells. Compound is reported to exhibit low toxicity in rats, with a maximum tolerated dose of 30 mg/kg i.v. or greater. Potentially useful for the treatment or prevention of immune disorders, asthma, neurodegeneration, hepatopathy, acute hepatitis, nephritis, renal insufficiency, hypertension, myocardial ischemia, sepsis, ulcerative colitis and sleep disorders. Other compounds from this series of 5-thia-ω-substituted phenyl-prostaglandin E derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
286045		-O-	H	CH2OMe	H	C ₂₃ H ₃₂ O ₆ S
286046		-O-	H	Me	OH	C ₂₂ H ₃₀ O ₆ S
286047	F	H	H	CH2OMe	H	C ₂₃ H ₃₃ FO ₆ S
286048		-O-	Me	CH2OEt	H	C ₂₆ H ₃₆ O ₆ S
286049		-O-	H	CH2OPr	H	C ₂₆ H ₃₆ O ₆ S



286050: C23 H34 O6 S

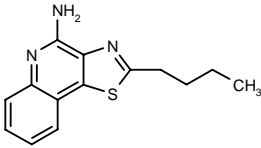
SOURCE – Ono.

REFERENCES

1. Maruyama, T. and Ohuchida, S. (Ono Pharmaceutical Co., Ltd.) *5-Thia-ω-substd. phenyl-prostaglandin E derivs., process for producing the same and drugs containing the same as the active ingredient*. WO 0003980.

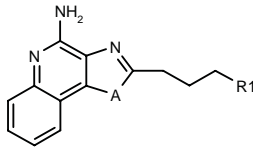
286235

2-Butylthiazolo[4,5-*c*]quinolin-4-amine



C14 H15 N3 S; Mol wt: 257.3595

ACTION – Immunomodulator and inducer of the biosynthesis of cytokines, particularly interferon alfa (IFN-α) and TNF-α, with potential in the treatment of cancer and viral diseases. *In vitro*, compound was shown to induce the production of IFN-α and TNF-α in human peripheral blood mononuclear cells (PBMCs) at concentrations of 1.11 and 0.12 μM, respectively. It is also reported to have an effect on the acquired immune response, in particular, to indirectly induce the production of the T-helper type 1 (Th1) cytokine interferon gamma and to inhibit the production of the T-helper type 2 (Th2) cytokines IL-4, IL-5 and IL-13, and thus may also be useful in the treatment of diseases where upregulation of the Th1 response and/or downregulation of the Th2 immune response is desired. Other compounds from this series of thiazolo-, oxazolo- and selenazolo[4,5-*c*]quinolin-4-amines include the following:



Compound	R1	A	Formula
286236	H	S	C ₁₃ H ₁₃ N ₃ S
286237	Me	O	C ₁₄ H ₁₅ N ₃ O

SOURCE – 3M Pharmaceuticals.

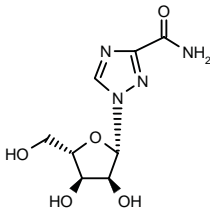
REFERENCES

1. Gerster, J.F. et al. (3M Pharmaceuticals) *Oxazolo, thiazolo and selenazolo[4,5-c]-quinolin-4-amines and analogs thereof*. WO 0006577.

ICN-17261

285605

1-(β-L-Ribofuranosyl)-1*H*-1,2,4-triazole-3-carboxamide



C8 H12 N4 O5; Mol wt: 244.2058

M.p. 177-9 °C; [*α*]_D²⁰ +35.3° (*c* 10, H₂O).

ACTION – Immunomodulating agent, the L-enantiomer of ribavirin with the ability to stimulate type 1 cytokine (IL-2, interferon gamma and TNF- α) production in staphylococcal enterotoxin B-activated human T-cells. Potentially useful for the treatment of diseases where type 1 cytokines play an important role such as viral diseases.

SOURCE – ICN.

REFERENCES

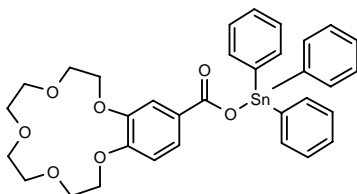
1. Ramasamy, K. et al. (ICN Pharmaceuticals, Inc.) *Monocyclic L-nucleosides, analogs and uses thereof*. WO 9816186.
2. Ramasamy, K.S. et al. *Monocyclic L-nucleosides with type 1 cytokine-inducing activity*. J Med Chem 2000, 43(5): 1019.
3. Tam, R.C. et al. *The ribavirin analog ICN 17261 demonstrates reduced toxicity and antiviral effects with retention of both immunomodulatory activity and reduction of hepatitis-induced serum alanine aminotransferase levels*. Antimicrob Agents Chemother 2000, 44(5): 1276.
4. ICN Pharmaceuticals, Inc. Annual Report 1998.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

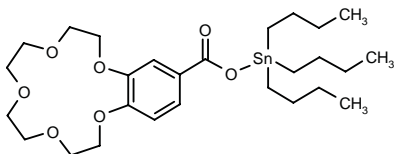
285803

(2,3,5,6,8,9,11,12-Octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-ylcarbonyloxy)(triphenyl)stannane



C33 H34 O7 Sn; Mol wt: 661.3346

ACTION – Antineoplastic agent with potent *in vitro* cytotoxicity against human mammary tumor MCF-7 and EVSA-T, colon carcinoma WiDr, ovarian cancer IGROV, melanoma M19 MEL, renal cancer A-498 and non-small cell lung cancer H226 cells, giving IC₅₀ values of < 3 ng/ml, being more potent than the known antitumor agents cisplatin, doxorubicin, etoposide, 5-fluorouracil and methotrexate. Compound is reported to be water-soluble. A representative compound from a series of tin polyoxaalkanecarboxylates, wherein the following is also included:



285804: C27 H46 O7 Sn

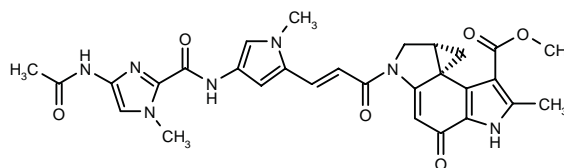
SOURCE – Pharmachemie.

REFERENCES

1. Gielen, M. et al. (Pharmachemie BV) *Tin polyoxaalkanecarboxylates and compsns. containing them*. WO 0006583.

285960

(3bS,4aR)-6-[3-[4-(Acetylamino)-1-methyl-1H-imidazol-2-ylcarboxamido]-1-methyl-1H-pyrrol-2-yl]-2(E)-propenoyl]-2-methyl-8-oxo-1,4,4a,5,6,8-hexahydrocyclopropa[c]pyrrolo[3,2-e]indole-3-carboxylic acid methyl ester



C29 H29 N7 O6; Mol wt: 571.5911

ACTION – DNA-dialkylating agent, a sequence-specific DNA-cleaving molecule able to alkylate both DNA strands at G/C base pairs.

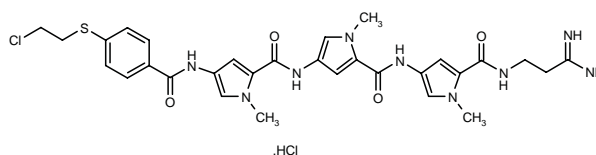
SOURCES – Kyoto University, Kyoto (JP); Tokyo Medical Dental University, Tokyo (JP).

REFERENCES

1. Tao, Z.-F. et al. *Highly cooperative DNA dialkylation by the homodimer of imidazole-pyrrole diamide - CPI conjugate with vinyl linker*. J Am Chem Soc 2000, 122(8): 1602.

286136

N-(2-Amidinoethyl)-4-[4-[4-(2-chloroethylsulfanyl)benz-amido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrole-2-carboxamide hydrochloride



C30 H34 Cl N9 O4 S . HCl; Mol wt: 688.6375

ACTION – Alkylating antitumor agent, a representative compound from a series of sulfurated distamycin A derivatives.

SOURCE – Pharmacia.

REFERENCES

1. Cozzi, P. et al. (Pharmacia & Upjohn SpA) *Sulfurated distamycin derivs., process for preparing them, and their use as antitumor agents*. WO 0006541.

ACTION – Immunomodulating agent, the L-enantiomer of ribavirin with the ability to stimulate type 1 cytokine (IL-2, interferon gamma and TNF- α) production in staphylococcal enterotoxin B-activated human T-cells. Potentially useful for the treatment of diseases where type 1 cytokines play an important role such as viral diseases.

SOURCE – ICN.

REFERENCES

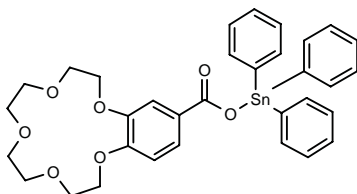
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ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

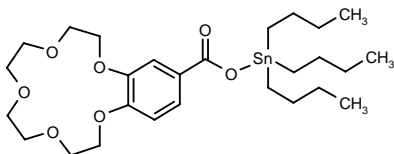
285803

(2,3,5,6,8,9,11,12-Octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-ylcarbonyloxy)(triphenyl)stannane



C33 H34 O7 Sn; Mol wt: 661.3346

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285804: C27 H46 O7 Sn

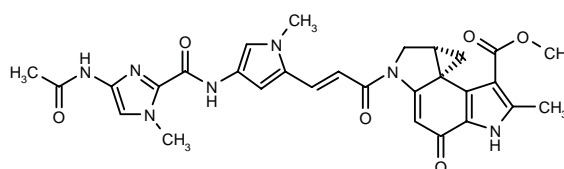
SOURCE – Pharmachemie.

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285960

(3bS,4aR)-6-[3-[4-(4-(Acetylamino)-1-methyl-1H-imidazol-2-ylcarboxamido)-1-methyl-1H-pyrrol-2-yl]-2(E)-propenoyl]-2-methyl-8-oxo-1,4,4a,5,6,8-hexahydrocyclopropa[c]pyrrolo[3,2-e]indole-3-carboxylic acid methyl ester



C29 H29 N7 O6; Mol wt: 571.5911

ACTION – DNA-dialkylating agent, a sequence-specific DNA-cleaving molecule able to alkylate both DNA strands at G/C base pairs.

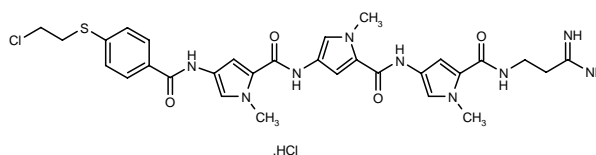
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286136

N-(2-Amidinoethyl)-4-[4-[4-(2-chloroethylsulfanyl)benz-amido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrole-2-carboxamide hydrochloride



C30 H34 Cl N9 O4 S . HCl; Mol wt: 688.6375

ACTION – Alkylating antitumor agent, a representative compound from a series of sulfurated distamycin A derivatives.

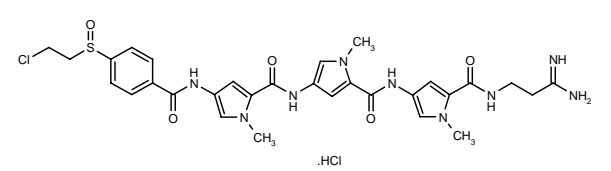
SOURCE – Pharmacia.

REFERENCES

1. Cozzi, P. et al. (Pharmacia & Upjohn SpA) *Sulfurated distamycin derivs., process for preparing them, and their use as antitumor agents*. WO 0006541.

286140

N-(2-Amidinoethyl)-4-[4-[4-(2-chloroethylsulfinyl)-benzamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrole-2-carboxamide hydrochloride



C30 H34 Cl N9 O5 S . HCl; Mol wt: 704.6365

ACTION – Alkylating antitumor agent, a representative compound from a series of oxidized sulfurated distamycin A derivatives.

SOURCE – Pharmacia.

REFERENCES

1. Cozzi, P. et al. (Pharmacia & Upjohn SpA) *Oxidised sulfurated distamycin derivs., process for preparing them, and their use as antitumor agents.* WO 0006542.

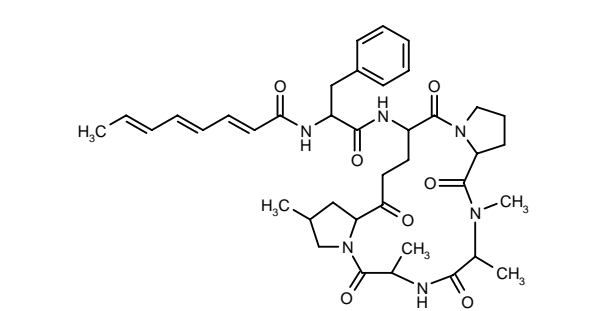
ANTIBIOTICS AND ALKALOIDS

BE-60828

286104

N-[1-[*N*-(2,6,9,10-Tetramethyl-5,8,11,16,20-pentaoxoperhydrodipyrrolo[1,2-*a*:1,2-*j*][1,4,7,10]tetraazacyclohexadecin-17-yl)carbamoyl]-2-phenylethyl]-2(*E*),4(*E*),6(*E*)-octatrienamamide

*N*²-[2(*E*),4(*E*),6(*E*)-Octatrienamido]-*N*¹-(2,6,9,10-tetramethyl-5,8,11,16,20-pentaoxoperhydrodipyrrolo-[1,2-*a*:1,2-*j*][1,4,7,10]tetraazacyclohexadecin-17-yl)-DL-phenylalaninamide



C39 H52 N6 O7; Mol wt: 716.8748

ACTION – Antineoplastic and antibacterial agent isolated from a culture of *Streptomyces* sp. A60828 (FERM P-16788) with *in vitro* cytotoxic activity against murine leukemia P388 (IC₅₀ = 2.8 µg/ml) and human lung cancer PC-13 (IC₅₀ = 5.0 µg/ml). Antibacterial activity was demonstrated against *Bacillus cereus* IFO 3001, *Staphylococcus aureus* FDA 209P and *Staphylococcus aureus* Smith (MIC = 0.78, 3.13 and 3.13 µg/ml, respectively).

SOURCE – Banyu.

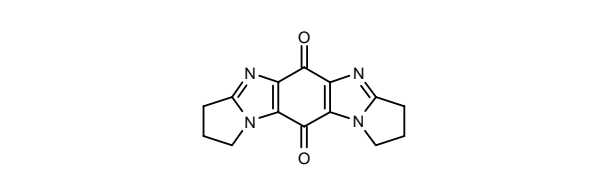
REFERENCES

1. Shimokawa, H. et al. (Banyu Pharmaceutical Co., Ltd.) *Anti-tumor substance BE-60828 and its preparation method.* JP 2000026497.

DNA-INTERCALATING DRUGS

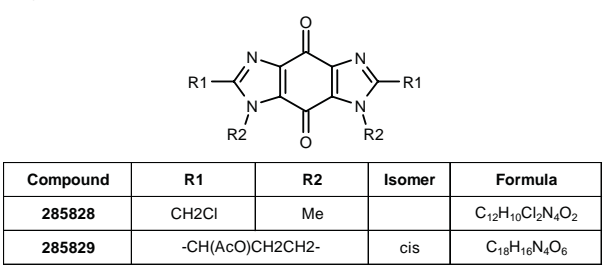
285827

2,3,7,8,9,11-Hexahydro-1*H*,5*H*-pyrrolo[1,2-*a*]pyrrolo-[1',2':1,2]imidazo[4,5-*f*]benzimidazole-5,10-dione



C14 H12 N4 O2; Mol wt: 268.2748

ACTION – Antineoplastic agent, an excellent substrate for DT-diaphorase with highly specific cytotoxic activity against melanoma cell lines. Compound was shown to inhibit topoisomerase II-mediated relaxation of supercoiled DNA. Other related quinones within this series of dipyrroloimidazobenzimidazole derivatives are:



SOURCE – Arizona State University, Tempe, AZ (US).

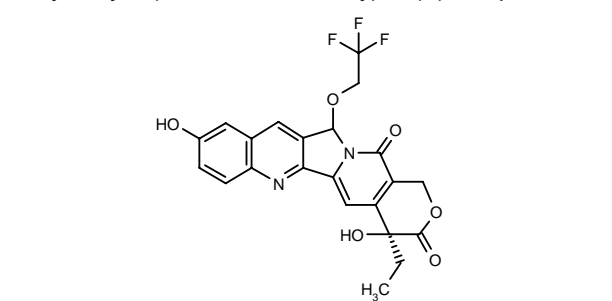
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286082

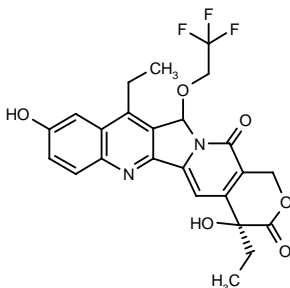
4(*S*)-Ethyl-4,9-dihydroxy-12-(2,2,2-trifluoroethoxy)-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione

10-Hydroxy-5-(2,2,2-trifluoroethoxy)-20(*S*)-camptothecin



C22 H17 F3 N2 O6; Mol wt: 462.3783

ACTION – Antineoplastic agent with cytotoxic activity against a number of human tumor cell lines including ovarian carcinoma OVCAR 8 (IC_{50} = 0.26 μ M), doxorubicin-resistant breast carcinoma MCF-7/ADR (IC_{50} = 0.20 μ M), prostate carcinoma DU 145 (IC_{50} = 0.10 μ M), renal carcinoma ACHN (IC_{50} = 0.10 μ M), lung carcinoma HOP62 (IC_{50} = 0.06 μ M), melanoma UACC62 (IC_{50} = 0.10 μ M) and CNS carcinoma SF 268 (IC_{50} = 0.03 μ M). *In vivo*, when given i.v. at doses of 90 and 134 mg/kg/day for 3 days, it was able to delay the growth of prostate (DU 145) and renal (A-498) tumor xenografts in nude mice. Another 5-substituted alkoxy 20(*S*)-camptothecin analogue is:



286083: C₂₄ H₂₁ F₃ N₂ O₆

SOURCE – Dr. Reddy's Research Foundation, Hyderabad (IN).

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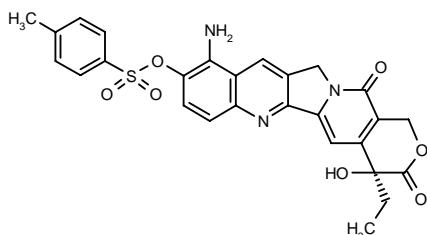
2. Subrahmanyam, D. et al. *Novel C-ring analogues of 20(S)-camptothecin. Part 3: Synthesis and their in vitro cytotoxicity of A-, B- and C-ring analogues*. Bioorg Med Chem Lett 2000, 10(4): 369.

FCE-28948

286501

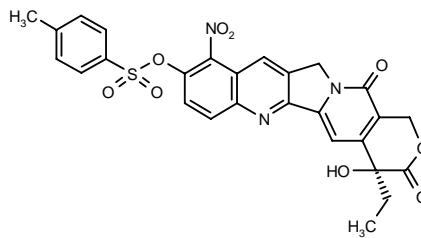
4-Methylbenzenesulfonic acid 10-amino-4(*S*)-ethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano-[3',4':6,7]indolizino[1,2-*b*]quinolin-9-yl ester

9-Amino-10-(4-methylphenylsulfonyloxy)-20(*S*)-camptothecin



C₂₇ H₂₃ N₃ O₇ S; Mol wt: 533.5587

ACTION – Antineoplastic camptothecin derivative found to possess cytotoxic activity against murine leukemia L1210 cells, with an IC_{50} value of 10.6 ng/ml. Another specifically claimed compound is:



FCE-28899 [286503]: C₂₇ H₂₁ N₃ O₉ S

SOURCE – Pharmacia.

REFERENCES

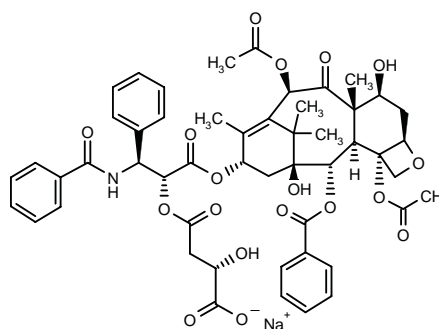
1. Cabri, W. et al. (Pharmacia & Upjohn SpA) *9-Amino- and 9-nitro-camptothecin derivs., process for their preparation and use as antitumor agents*. EP 0982307.

ANTIMITOTIC DRUGS

286137

2(*S*)-Hydroxy-4-oxo-4-(paclitaxel-2'-*O*-yl)butyric acid sodium salt

[2*aR*,4*S*,4*aS*,6*R*,9*S*(2'*R*,3'*S*),11*S*,12*S*,12*aR*,12*bS*]-3-Benzamido-2-[4-carboxy-3(*S*)-hydroxypropanoyloxy]-3-phenylpropionic acid 6,12*b*-diacetoxyl-12-(benzoyloxy)-4,11-dihydroxy-4*a*,8,13,13-tetramethyl-5-oxo-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-9-yl ester sodium salt



C₅₁ H₅₄ N Na O₁₈; Mol wt: 991.9666

ACTION – A prodrug of paclitaxel with improved water solubility, stable in solution at neutral pH and proven to generate paclitaxel when incubated in human plasma. Compared to paclitaxel, compound showed similar *in vitro* cytotoxicity but was more active and less toxic *in vivo* in mice bearing leukemia P388, where it produced a dose-dependent increase in survival time and had a higher therapeutic index than paclitaxel.

SOURCE – Pharmachemie.

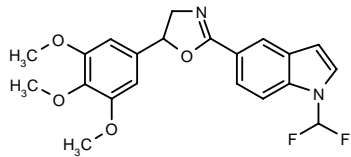
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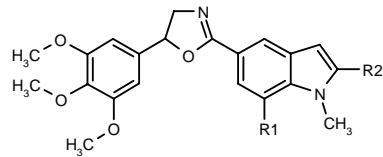
286191

1-(Difluoromethyl)-5-[5-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazol-2-yl]-1*H*-indole



C21 H20 F2 N2 O4; Mol wt: 402.3950

ACTION – Antineoplastic agent that is believed to act by disrupting the microtubule system, thereby inhibiting mitosis. Compound was shown to inhibit the proliferation of multidrug resistance (MDR)-positive human colon adenocarcinoma HCT-15 and MDR-negative human non-small cell lung carcinoma NCI-H460 cells with IC₅₀ values of 1.9 and 1.8 nM, respectively. Other specifically claimed compounds from this series of substituted oxazolines include the following:



Compound	R1	R2	Formula
286192	F	H	C ₂₁ H ₂₁ FN ₂ O ₄
286193	H	Me	C ₂₂ H ₂₄ N ₂ O ₄

SOURCE – Abbott.

REFERENCES

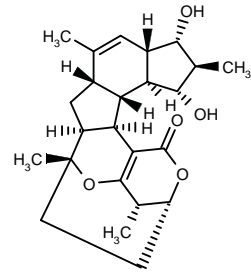
1. Gwaltney, S.L. II et al. (Abbott Laboratories Inc.) *Substd. oxazolines as antiproliferative agents*. WO 0006556.

FR-182877*

245094

(3*R*,4*S*,6*R*,6*aS*,7*aS*,9*aS*,10*S*,11*S*,12*R*,12*aS*,12*bS*,12*cR*)-10,12-Dihydroxy-4,6,8,11-tetramethyl-4,6,6*a*,7,7*a*,9*a*,10,11,12,12*a*,12*b*,12*c*-dodecahydro-1*H*,3*H*-3,6-etheno-as-indaceno[1,2-*d*]pyrano[4,3-*b*]pyran-1-one

WS-9885B



C24 H32 O5; Mol wt: 400.5118

ACTION – Antineoplastic agent isolated from the fermentation broth of *Streptomyces* sp. No. 9885, with cytotoxic activity against various human tumor cells such as non-small cell lung cancer A549, breast cancer MCF-7, colon cancer HT29 and Jurkat (leukemia) cells (IC₅₀ = 73, 27, 73 and 33 ng/ml, respectively), as well as against murine tumor cells including melanoma B16 and leukemia P388 cells (IC₅₀ = 67 and 21 ng/ml, respectively). Compound prolonged the survival time in mice bearing murine ascitic P388 tumors (T/C = 120-130% at 1.6-6.3 mg/kg/day i.p. on days 1, 4 and 7) and inhibited the growth of murine colon 38 tumors (T/C = 18-67% at 1-1.8 mg/kg/day i.v. for 4 days). It acts by promoting microtubule assembly and induces G2/M phase arrest in the cell cycle. The LD₅₀ in mice was determined to be > 60 mg/kg i.p.

SOURCE – Fujisawa.

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*Identified compound **FR-182877** (see **FR-182876**), published without structure in Drug Data Rep 1997, 019(03): 0267.

HORMONAL AGENTS

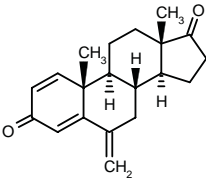
EXEMESTANE

Rec INN

129640

6-Methyleneandrosta-1,4-dien-3,17-dione

FCE-24304*



C20 H24 O2; Mol wt: 296.4076

ACTION – Antineoplastic agent, an irreversible steroidal aromatase inhibitor.

INDICATION – Treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following antiestrogen (tamoxifen) therapy.

PRESENTATION – Tablets, 25 mg.

PROPRIETARY NAME – Aromasin (CH, DE, FI, NO, SE, UK, US).

SOURCE – Pharmacia.

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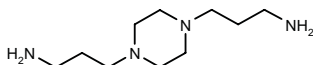
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CANCER IMMUNOTHERAPY

PI-Ca91

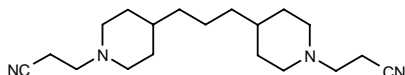
286247

1,4-Bis(3-aminopropyl)piperazine

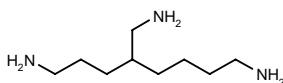


C10 H24 N4; Mol wt: 200.3276

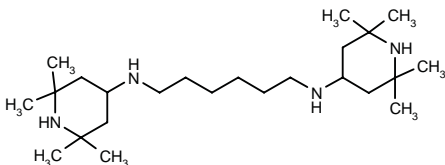
ACTION – Immunotherapeutic antineoplastic agent that acts as a spermine antagonist and is thus able to override the inhibitory effect of spermine on macrophage-mediated tumor killing and prevent spermine-induced immunosuppression. *In vitro*, compound was shown to reverse spermine-mediated inhibition of TNF synthesis in human peripheral blood mononuclear cells (PBMCs; $EC_{50} = 7 \pm 2.8 \mu M$) and to inhibit [^{14}C]-spermine uptake in lipopolysaccharide-stimulated human PBMCs ($IC_{50} = 8 \pm 3 \mu M$). In addition, compound was shown to restore the ability of tumor-associated macrophages to secrete TNF following administration to mice bearing B16F1 melanoma, and it induced extensive necrosis in the center of the tumors when given at 1.0 mg/kg/day i.p. x 7 days. Also, in mice with established B16F1 melanoma tumors, compound produced a significant reduction in tumor growth, providing complete inhibition in 40-60% of animals treated at a dose of 2.0 mg/kg i.p. x 8 days. Other exemplified compounds include the following:



PI-Ca92 [286248]: C19 H32 N4



PI-Ca94 [286249]: C9 H23 N3



PI-Ca38 [286250]: C24 H50 N4

SOURCE – Picower Institute for Medical Research, Manhasset, NY (US).

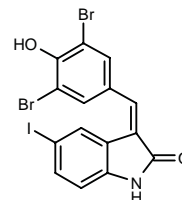
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INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

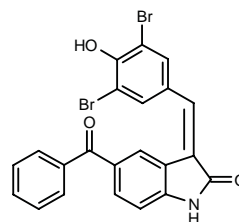
285752

3-(3,5-Dibromo-4-hydroxybenzylidene)-5-iodo-2,3-dihydro-1*H*-indol-2-one



C15 H8 Br2 I N O2; Mol wt: 520.9412

ACTION – Antineoplastic agent, a potent cRaf1 kinase inhibitor ($IC_{50} = 9 \text{ nM}$) with more than 100-fold selectivity versus CDK1, CDK2, c-src, ERK2, MEK, p38, Tie2, vascular endothelial growth factor (VEGF) type 2 receptor and c-fms kinases. Compound was able to block the intracellular MAP kinase pathway, as demonstrated by inhibition of epidermal growth factor (EGF)-stimulated MAP kinase activation in a cellular assay. It was shown to block the cell cycle in the G2 phase and to inhibit cell proliferation, anchorage-dependent growth and cell survival in reduced serum. In addition, it reduced the rate of tumor growth *in vivo* in mice bearing *ras*-transformed rat fibroblast cell lines. Within this series of cRaf1 inhibitors containing a pharmacophore composed of an acidic phenol and a donor/acceptor binding group (NH-CO), the following is also included:



285753: C22 H13 Br2 N O3

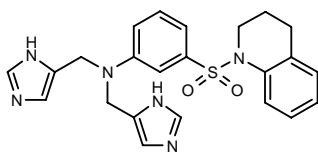
SOURCE – Glaxo Wellcome.

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285760

N-[3-(1,2,3,4-Tetrahydroquinolin-1-ylsulfonyl)phenyl]-*N,N*-bis(1*H*-imidazol-5-ylmethyl)amine



C23 H24 N6 O2 S; Mol wt: 448.5486

ACTION – Protein farnesyltransferase inhibitor (IC_{50} = 0.13 μ M), a small molecule not containing the problematic thiol and carboxylate functional groups.

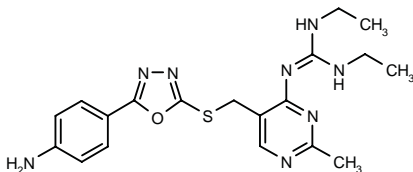
SOURCE – Bristol-Myers Squibb.

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285986

*N*²-[5-[5-(4-Aminophenyl)-1,3,4-oxadiazol-2-ylsulfonylmethyl]-2-methylpyrimidin-4-yl]-*N*¹,*N*³-diethylguanidine



C19 H24 N8 O S; Mol wt: 412.5196

ACTION – Antineoplastic agent that acts by inhibiting *ras* oncogene-mediated cell signaling at the level of the Ras responsive element (RRE). *In vitro*, compound was shown to inhibit the proliferation of human squamous cell lung cancer RERF-LC-AI and Ma44 and human colorectal carcinoma HT29 cells with IC_{50} values of 8.3, 49 and 11 ng/ml, respectively. *In vivo*, it inhibited tumor growth in mice bearing murine colon cancer Colon 26, human lung cancer RERF-LC-AI and Ma44 tumors (70, 74 and 66% inhibition, respectively, at 30 mg/kg/day p.o. x 14 days). A representative compound from a series of pyrimidine derivatives.

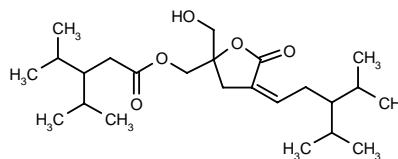
SOURCE – Shionogi.

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1. Ueda, K. et al. (Shionogi & Co. Ltd.) *Pyrimidine derivs. exhibiting antitumor activity*. WO 0004014.

286318

3-Isopropyl-4-methylpentanoic acid [2-(hydroxymethyl)-4-[(*Z*)-3-isopropyl-4-methylpentylidene]-5-oxo-tetrahydrofuran-2-yl]methyl ester



C24 H42 O5; Mol wt: 410.5908

ACTION – Antineoplastic agent, a diacylglycerol lactone with high binding affinity for protein kinase C (PKC; K_i = 2.9 nM), able to activate PKC (ED_{50} = 0.55 μ M) and inhibit epidermal growth factor (EGF) binding (EC_{50} = 0.17 μ M). Compound also bound to a newly characterized diacylglycerol receptor termed β_2 -chimaerin (IC_{50} = 0.9 nM). It exhibited cytotoxic activity in the NCI *in vitro* primary screen that consists of 60 different tumor cell lines, with a mean GI_{50} of 3.2 μ M; in particular, it showed nanomolar cytotoxic activity against leukemia K562, colon COLO 205 and breast Hs 578Tcell lines (GI_{50} = 25, 21 and 26 nM, respectively).

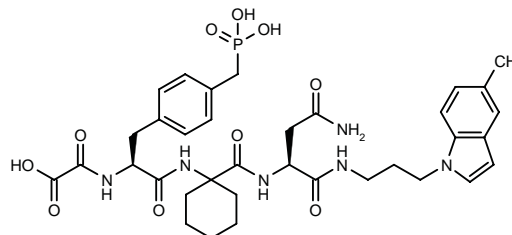
SOURCE – National Institutes of Health, Bethesda, MD (US).

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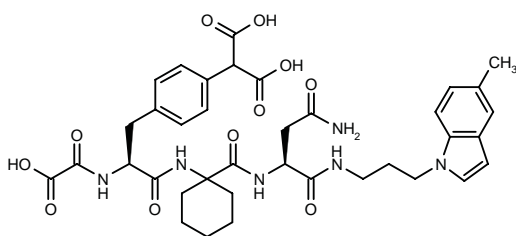
286394

N-(2-Hydroxy-1,2-dioxoethyl)-4-(phosphonomethyl)-L-phenylalanyl-(1-aminocyclohexylcarbonyl)-L-asparagine 3-(5-methyl-1*H*-indol-1-yl)propylamide



C35 H45 N6 O10 P; Mol wt: 740.7465

ACTION – Antineoplastic agent, an inhibitor of Grb2 (growth factor receptor-binding protein 2) SH2 domain binding (IC_{50} = 2 nM) with the ability to inhibit Grb2 association with the phosphorylated erbB-2 growth factor receptor and to activate MAP kinase in human breast cancer MDA-MB-453 cells. Within this series of phosphotyrosyl mimetics, the following is also described:



286395: C37 H44 N6 O11

SOURCES – Georgetown University, Washington, DC (US); National Cancer Institute, Bethesda, MD (US).

REFERENCES

1. Gao, Y. et al. *Inhibition of Grb2 SH2 domain binding by non-phosphate-containing ligands. 2. 4-(2-Malonyl)phenylalanine as a potent phosphotyrosyl mimetic.* J Med Chem 2000, 43(5): 911.

EGF-GENISTEIN

285640

Conjugate comprising epidermal growth factor (EGF) covalently linked to genistein via free amino groups in the peptide and the C-7 OH group in the flavone, in at least a 1:3 molar ratio

ACTION – Recombinant human epidermal growth factor (EGF) conjugated to the soybean-derived protein tyrosine kinase (PTK) inhibitor genistein, resulting in an EGF receptor-directed cytotoxic agent with PTK-inhibitory activity. The conjugate inhibited EGF receptor tyrosine kinase in MDA-MB-231 cells at submicromolar concentrations, whereas unconjugated genistein had no significant effect at up to 10 μ M. Compound was found to bind to and enter EGF receptor-positive human breast cancer MDA-MB-231 and BT-20 cells, but not EGF receptor-negative human leukemia cell lines. Rapid apoptotic cell death was observed in both breast cancer cell lines exposed to submicromolar concentrations of the compound, an effect which was dependent on both the PTK-inhibitory activity of genistein and the targeting function of EGF. In clonogenic assays, compound and free genistein gave IC_{50} values of 30 nM and 120 μ M, respectively, against MDA-MB-231 cells, and of 30 nM and 112 μ M, respectively, against BT-20 cells. The conjugate was thus shown to be over 100-fold more potent than unconjugated genistein in inhibiting EGF receptor TK activity and the growth of EGF receptor-positive breast cancer cells. *In vivo*, in SCID mice bearing human breast cancer MDA-MB-231 xenografts, compound (100 μ g/kg/day i.p. for 10 days) produced a 60% long-term tumor-free survival and was more effective than cyclophosphamide, doxorubicin or methotrexate. The conjugate was also highly effective in mice with established breast tumors, the same dose producing disappearance of tumors in 2 of 5 mice and over 50% tumor shrinkage in the other 3 animals; for comparison, animals treated with free genistein (1 mg/kg/day x 10) and controls showed an increase of over 200% in tumor diameter. A reduction in the growth rate of larger tumors was also observed. In cynomolgus monkeys, systemic exposure to doses higher than those effective in SCID mice were not associated with toxicity. Potentially useful as an antineoplastic agent for the treatment of cancers characterized by EGF receptor overexpression including prostate, ovarian, bladder, liver and lung cancer and melanoma, and also for the prevention of restenosis.

SOURCES – University of Minnesota, Minneapolis, MN (US); Parker Hughes Institute, St. Paul, MN (US).

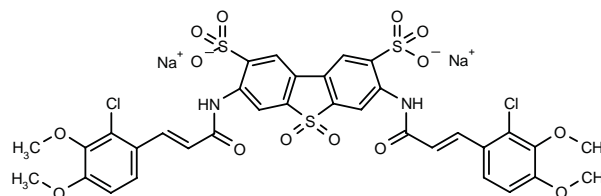
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ANGIOGENESIS INHIBITORS

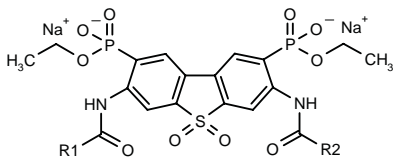
285631

3,7-Bis[3-(2-chloro-3,4-dimethoxyphenyl)-2(E)-propenamido]-5,5-dioxodibenzothiophene-2,8-disulfonic acid disodium salt



C34 H26 Cl2 N2 Na2 O14 S3; Mol wt: 899.6634

ACTION – Antiangiogenic agent that acts by inhibiting the binding of vascular endothelial growth factor (VEGF) and particularly isoform VEGF-165 to the receptors KDR and Flt-1, as demonstrated by IC_{50} values of 2.33 and 1.5 μ g/ml, respectively, for inhibition of [125 I]-VEGF binding to KDR and Flt-1 receptors in a scintillation proximity assay; in addition, compound inhibited the binding of [125 I]-VEGF to bovine aortic endothelial cells with an IC_{50} value of 0.37 μ g/ml. When tested *in vivo*, it inhibited the growth of human epidermoid A431 tumors in mice (T/C = 30%, 5/5 survivors on day 28 at 100 mg/kg p.o.), and it also significantly inhibited VEGF-induced vascular permeability in mice at 100 mg/kg p.o. Potentially useful for the treatment of conditions characterized by abnormal angiogenesis including ocular neovascular disease, neovascular glaucoma, diabetic retinopathy, fibroplasia, hemangiomas, angiofibromas, psoriasis, rheumatoid arthritis and solid tumor growth. Other compounds from this series of substituted dibenzothiophenes include the following:



Compound	R1,R2	Formula
285632	2-benzothienyl	C ₃₄ H ₂₆ N ₂ Na ₂ O ₁₀ P ₂ S ₃
285633	4-MeO-PhCH=CH	C ₃₆ H ₃₄ N ₂ Na ₂ O ₁₂ P ₂ S

SOURCE – American Home Products.

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1. Salvati, M.E. et al. (American Cyanamid Co.) *Substd. dibenzothiophenes having antiangiogenic activity*. US 6022307.

285639

19-Mer antisense oligodeoxynucleotide whose sequence is: 5'-GCGCTGATAGACATCCATG-3', in which the linkages between nucleosides 1-2, 2-3, 4-5, 7-8, 8-9, 11-12, 12-13, 14-15, 15-16, 16-17, 17-18 and 18-19 are phosphorothioate linkages

ACTION – Partially phosphorothioated 19-mer antisense oligodeoxynucleotide targeted at vascular endothelial growth factor (VEGF) with potential in the treatment of diseases associated with abnormal vascular permeability, cell proliferation, angiogenesis, neovascularization, tumor cell growth and/or metastasis. Compound was shown to potently and selectively inhibit VEGF mRNA and VEGF secretion *in vitro* (IC₅₀ = 100 and 300 nM, respectively). *In vivo*, it was found to dose-dependently reduce tumor growth in nude mice bearing U87-MG xenografts when administered at 4 and 12 mg/kg/day i.v., and it also markedly reduced VEGF mRNA levels in tumors and the size of vessels in tumors.

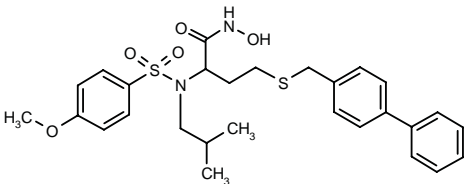
SOURCE – Aventis Pharma.

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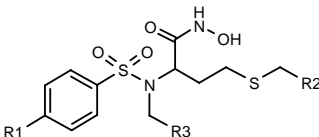
285867

4-(Biphenyl-4-ylmethylsulfanyl)-2-(*N*-isobutyl-4-methoxyphenylsulfonamido)butyroxamic acid



C28 H34 N2 O5 S2; Mol wt: 542.7176

ACTION – Matrix metalloproteinase inhibitor reported to have IC₅₀ values of 100-200 nM for MMP-1 (collagenase 1) and of 0.2-50 nM for MMP-2 (gelatinase A), MMP-3 (stromelysin 1) and MMP-9 (gelatinase B). Potentially useful in the treatment of a broad range of conditions, particularly cancer and rheumatic conditions such as arthrosis and rheumatoid arthritis. Other specifically claimed compounds from this series of hydroxamic acid derivatives include the following:



Compound	R1	R2	R3	Formula
285868	OMe	Ph	i-Pr	C ₂₂ H ₃₀ N ₂ O ₅ S ₂
285870	Ph	Ph	i-Pr	C ₂₇ H ₃₂ N ₂ O ₄ S ₂
285871	OMe	4-(PhCH2O)-Ph	i-Pr	C ₂₉ H ₃₆ N ₂ O ₆ S ₂
285872	Ph	H	i-Pr	C ₂₁ H ₂₈ N ₂ O ₄ S ₂
285873	OMe	Ph	CONHCH(Ph)2	C ₃₃ H ₃₅ N ₃ O ₆ S ₂

SOURCE – ADIR.

REFERENCES

1. Hanessian, S. et al. (ADIR et Cie.) *Hydroxamic acid derivs., process for their preparation and pharmaceutical compsns. containing them*. EP 0979816, FR 2782080, JP 2000086618.

286398

12-Mer antisense oligonucleotide whose sequence is: 3'-GGGTCCGACGTG-5', in which the linkages between nucleotides 1-2, 3-4, 4-5, 5-6, 9-10 and 11-12 are phosphorothioate

ACTION – Antisense oligonucleotide, a representative compound from a series of short oligonucleotides with a sequence corresponding to a particular part of the nucleic acid sequence encoding vascular endothelial growth factor (VEGF) and having a maximum length of 15 nucleotides. *In vitro*, compound inhibited VEGF mRNA expression (about 80% at 3 μM) and VEGF protein secretion (IC₅₀ = 0.55 μM) in U87-MG tumor cells. *In vivo*, it was found to inhibit tumor growth in nude mice bearing U87-MG xenografts at 12 mg/kg/day i.v. x 4 days. Potentially useful in the treatment of diseases associated with abnormal vascular permeability, cell proliferation, cell permeation, angiogenesis, neovascularization, tumor cell growth and/or metastasis.

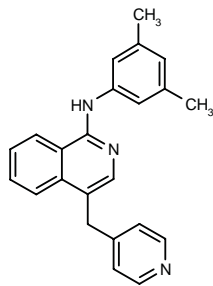
SOURCE – Aventis Pharma.

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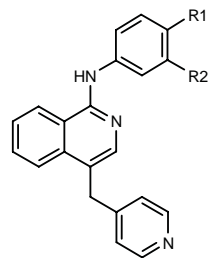
286476

N-(3,5-Dimethylphenyl)-N-[4-(4-pyridinylmethyl)-isoquinolin-1-yl]amine



C23 H21 N3; Mol wt: 339.4399

ACTION – An inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinase (IC_{50} = 0.802 μ M against Flt-1 VEGF receptor tyrosine kinase) and VEGF-dependent cell proliferation, with potential in the treatment of diseases associated with deregulated angiogenesis, especially proliferative diseases such as tumors. Other exemplified compounds from this series of isoquinoline derivatives include the following:



Compound	R1	R2	Formula
286477	Cl	H	C ₂₁ H ₁₆ ClN ₃
286478	H	Me	C ₂₂ H ₁₉ N ₃

SOURCE – Novartis.

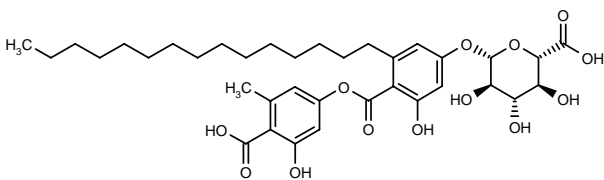
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CRM-646-A

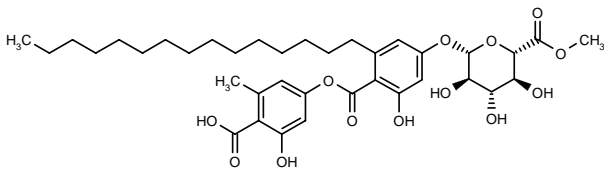
286023

1-O-[4-(4-Carboxy-3-hydroxy-5-methylphenoxy)carbonyl]-3-hydroxy-5-pentadecylphenoxy]- β -D-glucopyranuronic acid



C36 H50 O13; Mol wt: 690.7780

ACTION – Fungal metabolite extracted from *Acremonium* sp. MT70646 with potent and selective heparinase-inhibitory activity (IC_{50} = 3 μ M), comparable to suramin (IC_{50} = 5 μ M). It exhibited strong antimetastatic activity *in vitro* (IC_{50} = 15 μ M against melanoma B16-F10 cell migration) but only negligible cytotoxic activity against various cells at up to 100 μ M. Another related compound is:



CRM-646-B [286025]: C37 H52 O13

SOURCES – Institute of Physical and Chemical Research (RIKEN), Saitama (JP); Korea Research Institute of Bio-science and Biotechnology, Taedok Science Town (KR).

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1. Ko, H.R. et al. *CRM646-A and -B, novel fungal metabolites that inhibit heparinase*. J Antibiot 2000, 53(2): 211.

NEOVASTAT®

232147

Standardized liquid extract from shark cartilage

AE-941

ACTION – Antineoplastic agent, a standardized extract from shark cartilage with antiangiogenic activity, proven to inhibit matrix metalloproteinases (MMP-2, MMP-9 and MMP-12) and to have affinity for vascular endothelial growth factor (VEGF) receptors. Oral administration of compound (500 mg/kg) to mice grafted with mouse mammary adenocarcinoma DA3 or Lewis lung carcinoma resulted in a significant decrease of 60 and 71% in tumor volume and lung nodules, respectively; an 83% reduction in nodule number was observed on combined treatment with compound (500 mg/kg p.o.) and cisplatin (3 mg/kg i.p.) as compared to 54% on cisplatin alone. Compound is currently under clinical investigation for the treatment of lung, prostate and breast cancer, refractory solid tumors and age-related macular degeneration.

SOURCES – AEterna; Alcon.

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OTHER ONCOLYTIC DRUGS

285634

L-Glutamyl-L-alanyl-L-arginyl-L-prolyl-L-alanyl-L-leucyl-L-leucyl-L-threonyl-L-seryl-L-arginyl-L-leucyl-L-arginyl-L-phenylalanyl-L-isoleucyl-L-prolyl-L-lysine

C85 H146 N26 O21; Mol wt: 1868.2490

ACTION – Antigenic peptide for the treatment of cancer derived from telomerase that acts by generating a T-cell response against telomerase, which has been detected in the majority of cancers; since most cells in the body do not express telomerase, they will be unaffected, whereas tumor cells expressing telomerase will be targeted and destroyed. Other compounds from this series of telomerase-derived peptides include the following:

L-Aspartyl-glycyl-L-leucyl-L-arginyl-L-prolyl-L-isoleucyl-L-valyl-L-asparaginyl-L-methionyl-L-aspartyl-L-tyrosyl-L-valyl-L-valyl-glycyl-L-alanyl-L-arginine

285635: C77 H127 N23 O23 S

Glycyl-L-valyl-L-prolyl-L-glutamyl-L-tyrosyl-glycyl-L-cysteinyl-L-valyl-L-asparaginyl-L-leucyl-L-arginyl-L-lysyl-L-threonyl-L-valyl-L-valyl-L-asparaginyl-L-phenylalanine

285636: C90 H144 N24 O25 S

L-Leucyl-L-methionyl-L-seryl-L-valyl-L-tyrosyl-L-valyl-L-glutamyl-L-leucyl-L-leucyl-L-arginyl-L-seryl-L-phenylalanyl-L-phenylalanyl-L-tyrosyl-L-valyl-L-threonyl-L-glutamic acid

285637: C105 H159 N21 O28 S

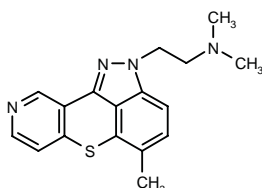
SOURCE – Norsk Hydro.

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285773

2-[2-(Diethylamino)ethyl]-5-methyl-2*H*-pyrido[3',4':5,6]-thiopyrano[4,3,2-*cd*]indazole



C17 H18 N4 S; Mol wt: 310.4232

ACTION – Antineoplastic agent with strong cytotoxic activity against several different cancer cell lines including murine leukemia L1210, murine sarcoma S-180, human colon adenocarcinoma LoVo (IC₅₀ = 0.6, 3 and 4 ng/ml, respectively) and doxorubicin-resistant S-180 and LoVo cells (IC₅₀ = 9 and 18 nM, respectively). Selected for further evaluation for *in vivo* antitumor activity and topoisomerase II inhibition.

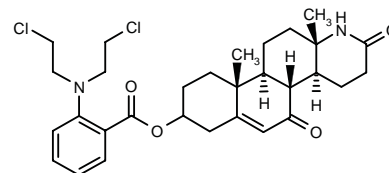
SOURCE – Novuspharma.

REFERENCES

1. Krapcho, A.P. et al. *Synthesis and antitumor activities of 5-methyl-1- and 2-[[2-dimethylaminoethyl]amino]-aza-thiopyranoindazoles*. Bioorg Med Chem Lett 2000, 10(3): 305.

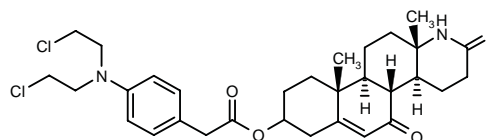
285941

2-[Bis(2-chloroethyl)amino]benzoic acid (4*aS*,4*bR*,10*aR*,10*bS*,12*aS*)-10*a*,12*a*-dimethyl-2,5-dioxo-1,2,3,4,4*a*,4*b*,5,7,8,9,10,10*a*,10*b*,11,12,12*a*-hexadecahydronaphtho-[2,1-*f*]quinolin-8-yl ester



C30 H38 Cl2 N2 O4; Mol wt: 561.5462

ACTION – Antineoplastic agent proven to increase life span of mice bearing murine leukemia P388 when administered i.p. at doses of 87.5 mg/kg as 9 daily injections, 175 mg/kg as 3 injections on days 1, 5 and 9, or 350 mg/kg as a single injection; intermittent treatment (days 1, 5 and 9) showed the best antitumor efficacy. Compound displayed low acute toxicity in mice, with an LD₅₀ value of 600 mg/kg i.p. Another modified steroidal lactam is:



285942: C31 H40 Cl2 N2 O4

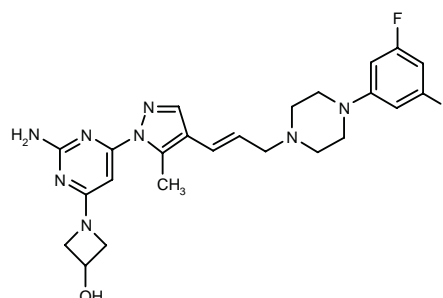
SOURCES – University of Patras, Patras (GR); Theagenio Cancer Hospital, Thessaloniki (GR).

REFERENCES

1. Papageorgiou, A. et al. *In the search for new anticancer drugs: Modified steroidal lactams of amino phenylacetate and amino benzoate*. 10th Int Congr Anti-Cancer Treat (Jan 31-Feb 3, Paris) 2000, Abst P261.

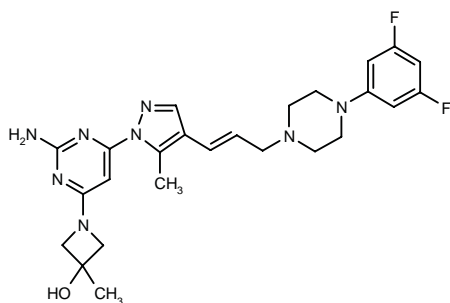
285989

1-[2-Amino-6-[4-[3-[4-(3,5-difluorophenyl)piperazin-1-yl]-1(*E*)-propenyl]-5-methyl-1*H*-pyrazol-1-yl]pyrimidin-4-yl]-azetidin-3-ol



C24 H28 F2 N8 O; Mol wt: 482.5362

ACTION – Antineoplastic agent with potent growth-inhibitory activity against human lung cancer PC-12 cells (GI₅₀ = 0.601 ng/ml); it was active *in vivo* in mice bearing s.c.-transplanted murine fibrosarcoma Meth A tumors. Another compound from this series of pyrazole derivatives is:



285990: C₂₅ H₃₀ F₂ N₈ O

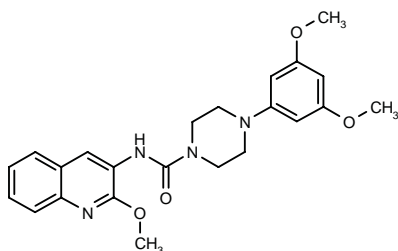
SOURCE – Daiichi Pharmaceutical.

REFERENCES

1. Ejima, A. et al. (Daiichi Pharmaceutical Co., Ltd.) *Pyrazole derivs. and salts thereof*. WO 0005230.

286024

4-(3,5-Dimethoxyphenyl)-*N*-(2-methoxyquinolin-3-yl)piperazine-1-carboxamide



C₂₃ H₂₆ N₄ O₄; Mol wt: 422.4824

ACTION – Antineoplastic agent with potent cytotoxicity against human non-small cell lung cancer A549, ovarian cancer SKOV-3, colon cancer HCT-15, CNS cancer XF 498 and melanoma SKMEL-2 cell lines, giving respective EC₅₀ values of 0.0032, 0.0007, 0.0054, 0.0097 and 0.0107 µg/ml and being more potent than cisplatin (EC₅₀ = 0.8184, 0.7134, 3.0381, 0.7771 and 0.7147 µg/ml, respectively) and doxorubicin (EC₅₀ = 0.0168, 0.0176, 1.6689, 0.0250 and 0.0108 µg/ml, respectively). When tested *in vivo* in mice bearing leukemia P388, it was found to significantly increase survival of animals, giving T/C values of 218.2% at a dose of 200 mg/kg intraabdominally on days 1, 5 and 9, and of 210.0% at a dose of 50 mg/kg/day x 9 days. Acute toxicity testing in mice showed an LD₅₀ of 1600 mg/kg i.p. compared to an LD₅₀ for cisplatin of 9.7 mg/kg i.p.

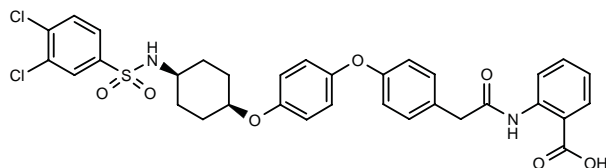
SOURCE – Samjin.

REFERENCES

1. Cho, E.-H. et al. (Samjin Pharmaceutical Co., Ltd.) *Piperazine derivs. and process for the preparation thereof*. US 6028195, WO 9800402.

286027

cis-2-[2-[4-[4-[4-(3,4-Dichlorophenylsulfonamido)-cyclohexyloxy]phenoxy]phenyl]acetamido]benzoic acid



C₃₃ H₃₀ Cl₂ N₂ O₇ S; Mol wt: 669.5790

ACTION – Antineoplastic agent that also exhibits IgE antibody production-inhibitory activity and may therefore also be used in the treatment or prevention of allergic diseases. Compound displayed an LD₅₀ value of 0.14 µM against murine L929 tumor cells and was further tested against a panel of human tumor cell lines, giving GI₅₀ values ranging from 0.086 to 10 µM. A representative compound from a series of anthranilic acid derivatives.

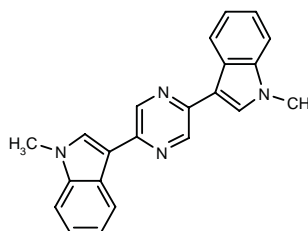
SOURCE – Teijin.

REFERENCES

1. Tsuchiya, N. et al. (Teijin Ltd.) *Anthranilic acid derivs*. WO 0005198.

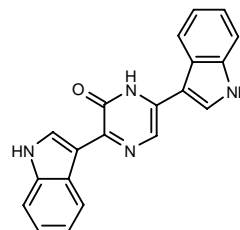
286122

2,5-Bis(1-methyl-1*H*-indol-3-yl)pyrazine



C₂₂ H₁₈ N₄; Mol wt: 338.4122

ACTION – Antineoplastic agent, an analogue of a marine bis(indole) alkaloid with strong growth-inhibitory activity against a panel of human cancer cell lines including lung NCI-H322M, colon HCT-15 and KM12, melanoma SK-MEL-5 and breast MCF-7 cells (IC₅₀ = 0.72, 0.248, 0.058, 0.287 and 0.29 µM, respectively). Another related compound is:



286124: C₂₀ H₁₄ N₄ O

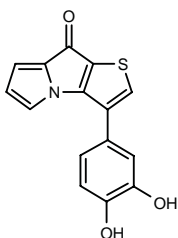
SOURCE – Chinese Academy of Sciences, Beijing (CN).

REFERENCES

1. Jiang, B. and Gu, X.-H. *Syntheses and cytotoxicity evaluation of bis(indolyl)thiazole, bis(indolyl)pyrazinone and bis(indolyl)pyrazine: Analogues of cytotoxic marine bis(indole) alkaloid*. *Bioorg Med Chem* 2000, 8(2): 363.

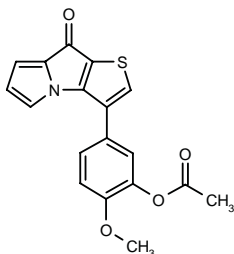
286545

3-(3,4-Dihydroxyphenyl)-8*H*-thieno[2,3-*b*]pyrrolizine-8-one



C₁₅ H₉ N O₃ S; Mol wt: 283.3061

ACTION – Antineoplastic agent reported to be particularly useful for the treatment of solid tumors. Compound exhibited potent cytotoxicity against murine leukemia P388 and L1210, human non-small cell lung carcinoma A549, human epidermoid carcinoma KB-3-1 and its multidrug-resistant variant KB-A1, and human ovarian carcinoma IGROV1 cells, with IC₅₀ values of 356, 222, 122, 33, 22 and 56 nM, respectively, thus showing stronger activity against human solid tumor cell lines. In addition, compound was also shown to induce accumulation of cells in the G2/M phase (80-90% of cells following incubation for 21 h at a concentration of 500 nM). *In vivo*, it increased the survival of mice bearing murine P388 leukemia by 70% at a dose of 25 mg/kg/day i.p., as well as the survival of nude mice bearing human IGROV1 xenografts by 60% at a dose of 200 mg/kg i.p. Another specifically claimed compound from this series of 8*H*-[2,3-*b*]pyrrolizin-8-one derivatives is:



286546: C₁₆ H₁₁ N O₂ S

SOURCE – ADIR.

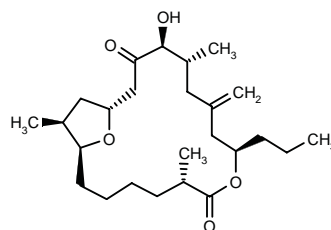
REFERENCES

1. Rault, S. et al. (ADIR et Cie.) *Derivs. of the 8H-(2,3-b)-pyrrolizine-8-one, process for their preparation and pharmaceutical compsns. containing them*. EP 0982308, FR 2781482, JP 2000044572.

AMPHIDINOLIDE T

286208

(1*SR*,6*S*,9*R*,13*R*,14*S*,17*RS*,19*SR*)-14-Hydroxy-6,13,19-trimethyl-11-methylened-9-propyl-8,20-dioxabicyclo[15.2.1]icosane-7,15-dione



C₂₅ H₄₂ O₅; Mol wt: 422.6018

ACTION – Antineoplastic agent, a 19-membered macrolide extracted from the marine dinoflagellate *Amphidinium* sp., with cytotoxic activity against murine leukemia L1210 cells (IC₅₀ = 18 µg/ml).

SOURCE – Hokkaido University, Sapporo (JP).

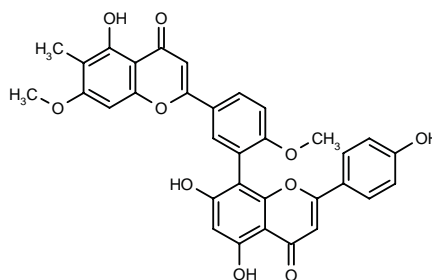
REFERENCES

1. Tsuda, M. et al. *Amphidinolide T, novel 19-membered macrolide from marine dinoflagellate Amphidinium sp.* *J Org Chem* 2000, 65(5): 1349.

TAIWANHOMOFLAVONE A

286562

2-[3-[5,7-Dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4*H*-1-benzopyran-8-yl]-4-methoxyphenyl]-5-hydroxy-7-methoxy-6-methyl-4*H*-1-benzopyran-4-one



C₃₃ H₂₄ O₁₀; Mol wt: 580.5426

ACTION – Antineoplastic agent, a *C*-methylated biflavone extracted from the stem of *Cephalotaxus wilsoniana*, an evergreen tree found in the mountains of Taiwan. Cytotoxic activity was seen against human cancer cell lines such as nasopharyngeal epidermoid carcinoma KB, colon carcinoma COLO-205, hepatoma Hepa-3B and cervix HeLa cells (IC₅₀ = 3.4, 1, 2 and 2.5 µg/ml, respectively).

SOURCES – Chinese Culture University, Taipei (TW); National Research Institute of Chinese Medicine, Taipei (TW).

REFERENCES

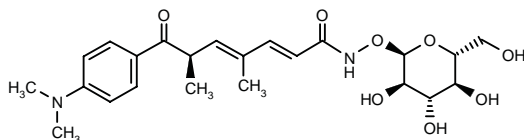
1. Kuo, Y.-H. et al. *A novel cytotoxic C-methylated biflavone from the stem of Cephalotaxus wilsoniana*. *Chem Pharm Bull* 2000, 48(3): 440.

TRICHOSTATIN D

286017

7-[4-(Dimethylamino)phenyl]-4,6(*R*)-dimethyl-7-oxo-*N*-(α -D-glucopyranosyloxy)-2(*E*),4(*E*)-heptadienamide

JS-49



C23 H32 N2 O8; Mol wt: 464.5118

ACTION – Antineoplastic agent extracted from the actinomycete *Streptomyces violaceusniger*, able to induce phenotypic reversion in transformed cells such as NIH3T3 murine fibroblasts transformed with human papilloma oncogene (NIH3T3/T-601 cells) and NIH3T3 cells transformed with H-ras or *hst-1* (NIH3T3/ras and NIH3T3/*hst-1* cells, respectively). Compound was also able to inhibit the growth of NIH3T3/T-601 cells (IC_{50} = 33 ng/ml) and colony formation in soft agar.

SOURCE – Kirin Brewery.

REFERENCES

1. Seto, H. and Hayakawa, Y. (Kirin Brewery Co., Ltd.) *Novel cpd. JS49, its use and preparation method.* JP 1994100582.

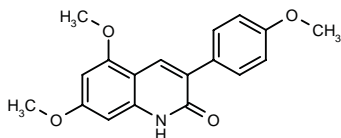
2. Hayakawa, Y. et al. *Trichostatin D, a new inducer of phenotypic reversion in transformed cells.* J Antibiot 2000, 53(2): 179.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

CRL-8246

285566

5,7-Dimethoxy-3-(4-methoxyphenyl)quinolin-2(1*H*)-one



C18 H17 N O4; Mol wt: 311.3353

ACTION – Agent for use in the treatment of cancer in combination with conventional cytotoxic drugs that acts by stimulating the recruitment of clonogenic cells in tumors, thus increasing the sensitivity of the tumor to the antineoplastic agent. When tested *in vivo* in mice bearing murine hormone-sensitive mammary adenocarcinoma MXT-HS tumors, compound was shown to potentiate the effects of cyclophosphamide, etoposide and doxorubicin while showing no effect when given alone. Furthermore, coadministration of compound (40 mg/kg/day i.v.) and vincristine (0.63 mg/kg/day i.v.) significantly increased the survival time of mice bearing murine leukemia P388 (T/C = 144% vs. 122% for vincristine alone). A representative compound from a series of 2-quinolone derivatives.

SOURCE – Lafon.

REFERENCES

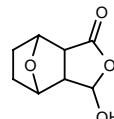
1. Joseph, B. et al. (Laboratoires L. Lafon) *Pharmaceutical compsns. comprising 2-quinolones.* FR 2781218, WO 0003990.

MK-4

285557

5-Hydroxy-4,10-dioxatricyclo[5.2.1.0^{2,6}]decan-3-one

4,7-Epoxy-3-hydroxyperhydroisobenzofuran-1-one



C8 H10 O4; Mol wt: 170.1630

ACTION – Antineoplastic agent, an inhibitor of protein phosphatases 1 and 2A (PP1 and PP2A) that is reported to be cell-permeable and stable to oxidation; compound is able to abrogate the G1 or G2 cell cycle checkpoint and prematurely force cells through the cell cycle, which is expected to result in enhancement of the cytotoxicity of other anticancer therapies by preventing the repair of DNA damage. Compound exhibited cytotoxicity to several tumor cell lines, particularly human colon cancer cell lines, with IC_{50} values in the range of 14-88 μ M. It was also shown to induce G2 arrest and to abrogate G1 arrest in murine leukemia L1210, human leukemia HL-60 and human colon cancer HCT 116 cells, and it abrogated the G2 checkpoint in human colon HT-29 cells, the cell line against which it exhibited greatest cytotoxicity. Furthermore, simultaneous combination with cisplatin provided an additive cytotoxic response in HCT 116 and HT-29 cells, while combination with docetaxel was additive in HT-29 cells and synergistic in HCT 116 cells. A representative compound from a series of anhydride modified cantharidin analogues.

SOURCE – University of Newcastle at Australia, Newcastle, NS (AU).

REFERENCES

1. McCluskey, A. et al. (University of Newcastle at Australia) *Anhydride modified cantharidin analogues useful in the treatment of cancer.* WO 0004023.

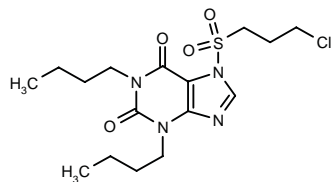
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

285841

1,3-Dibutyl-7-(3-chloropropylsulfonyl)-3,7-dihydro-1*H*-purine-2,6-dione

1,3-Dibutyl-7-(3-chloropropylsulfonyl)xanthine



C16 H25 Cl N4 O4 S; Mol wt: 404.9165

M.p. 71-3 °C.

ACTION – Agent for the treatment of osteoporosis, a calcitonin (CT) inducer proven to stimulate CT transcription (2.1-fold increase at 30 μM in a CT-luciferase reporter gene assay) and CT secretion (3.6-fold increase at 30 μM). Moreover, compound showed moderate inhibitory activity against phosphodiesterase type 4 (PDE4; IC₅₀ = 4.1 μM). *In vivo*, an oral dose of 50 mg/kg/day for 3 weeks was associated with a significant trabecular bone-sparing effect (50%) in ovariectomized osteopenic rats. Potentially useful for the treatment of conditions characterized by bone loss.

SOURCES – OSI; Wyeth-Ayerst.

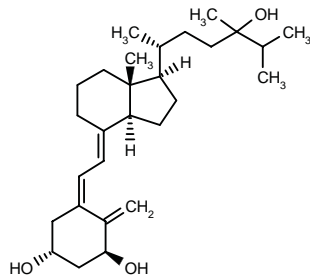
REFERENCES

1. Gilbert, A.M. et al. *Novel and selective calcitonin-inducing agents*. J Med Chem 2000, 43(6): 1223.

285862

1α,24-Dihydroxyvitamin D₄

1α,24-Dihydroxy-24-methylvitamin D₃



C28 H46 O3; Mol wt: 430.6684

ACTION – Metabolite of 1α-hydroxy vitamin D₄ reported to be useful for increasing serum calcium levels in patients with vitamin D deficiency, as well as to exhibit low toxicity.

Studies using 1α-hydroxy vitamin D₄ demonstrated that it increases serum calcium in vitamin D-deficient rats, but not in animals fed a calcium-containing diet, and that it stimulates intestinal calcium transport in rats fed a vitamin D-deficient, low-calcium diet. Clinical trials in postmenopausal osteoporotic patients demonstrated its ability to significantly increase bone densities and stimulate normal bone formation without significant hypercalcemia or hypercalciuria, and also that it is able to reduce loss of bone density in healthy postmenopausal women.

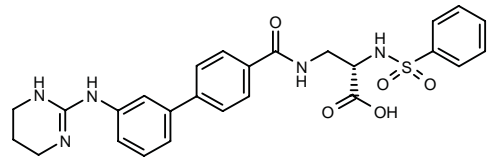
SOURCE – Bone Care International.

REFERENCES

1. Knutson, J.C. et al. (Bone Care International, Inc.) *1α-Hydroxy vitamin D4 and novel intermediates and analogues*. US 6025346.

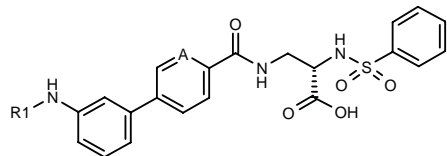
286170

2(*S*)-(Phenylsulfonylamido)-3-[3'-(1,4,5,6-tetrahydropyrimidin-2-ylamino)biphenyl-4-ylcarboxamido]propionic acid

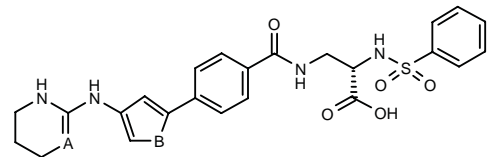


C26 H27 N5 O5 S; Mol wt: 521.5953

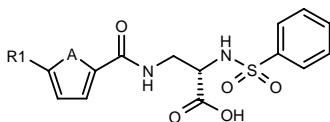
ACTION – Nonpeptide integrin, particularly α_vβ₃, α_vβ₅ and/or α_vβ₆, receptor antagonist, potentially useful for inhibiting bone resorption and restenosis and for the treatment or prevention of osteoporosis, atherosclerosis, inflammation, inflammatory arthritis, viral disease, diabetic retinopathy, macular degeneration, angiogenesis and tumor growth and metastasis. Other specifically claimed compounds from this series of biaryl derivatives include the following:



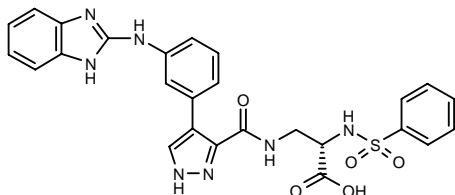
Compound	R1	A	Formula
286171	5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl	CH	C ₃₀ H ₂₉ N ₅ O ₅ S
286173	2-benzimidazolyl	N	C ₂₈ H ₂₄ N ₆ O ₅ S
286178	2-pyrimidinyl	CH	C ₂₆ H ₂₃ N ₅ O ₅ S



Compound	A	B	Formula
286172	CH	S	C ₂₅ H ₂₆ N ₄ O ₅ S ₂
286174	N	O	C ₂₄ H ₂₅ N ₅ O ₆ S



Compound	R1	A	Formula
286175	4-(2-imidazolyl-NH)- -2-thienyl	S	C ₂₁ H ₁₉ N ₅ O ₅ S ₃
286177	5-(1,4,5,6-tetrahydro- -2-pyrimidinyl-NH)-2-thienyl	O	C ₂₂ H ₂₃ N ₅ O ₆ S ₂



286176: C₂₆ H₂₃ N₇ O₅ S

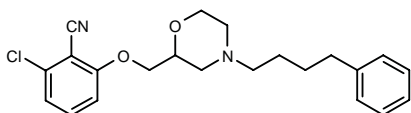
SOURCE – Merck & Co.

REFERENCES

1. Duggan, M.E. and Hartman, G.D. (Merck & Co., Inc.) *Integrin receptor antagonists*. US 6040311, WO 0006169.

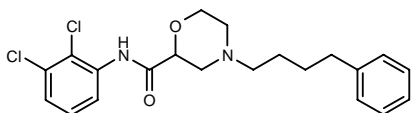
286459

2-Chloro-6-[4-(4-phenylbutyl)morpholin-2-ylmethoxy]-benzonitrile



C₂₂ H₂₅ Cl N₂ O₂; Mol wt: 384.9045

ACTION – Calcilytic compound that acts as a calcium receptor antagonist and which can be used to increase serum parathyroid hormone (PTH) levels. Potentially useful in the treatment of diseases associated with abnormal bone or mineral homeostasis such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and osteoporosis. Another specifically claimed compound from this series of morpholine derivatives is:



286460: C₂₁ H₂₄ Cl₂ N₂ O₂

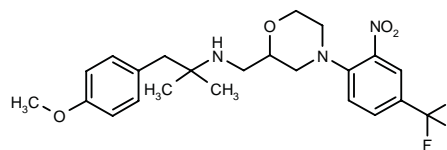
SOURCE – SmithKline Beecham.

REFERENCES

1. Bhatnagar, P.K. and Lago, A.M. (SmithKline Beecham Corp.) *Calcilytic cpds*. WO 0009491.

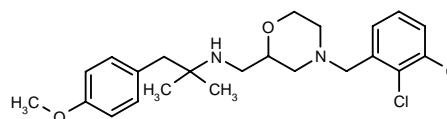
286462

N-[2-(4-Methoxyphenyl)-1,1-dimethylethyl]-*N*-[4-[2-nitro-4-(trifluoromethyl)phenyl]morpholin-2-ylmethyl]amine



C₂₃ H₂₈ F₃ N₃ O₄; Mol wt: 467.4852

ACTION – Calcilytic compound that acts as a calcium receptor antagonist and can be used to increase serum parathyroid hormone (PTH) levels. Potentially useful in the treatment of diseases associated with abnormal bone or mineral homeostasis such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and osteoporosis. Another specifically claimed compound from this series of morpholine derivatives is:



286463: C₂₃ H₃₀ Cl₂ N₂ O₂

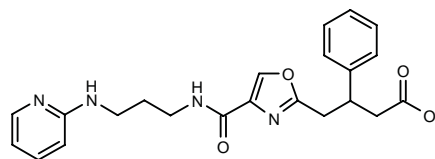
SOURCE – SmithKline Beecham.

REFERENCES

1. Bhatnagar, P.K. and Lago, A.M. (SmithKline Beecham Corp.) *Calcilytic cpds*. WO 0009132.

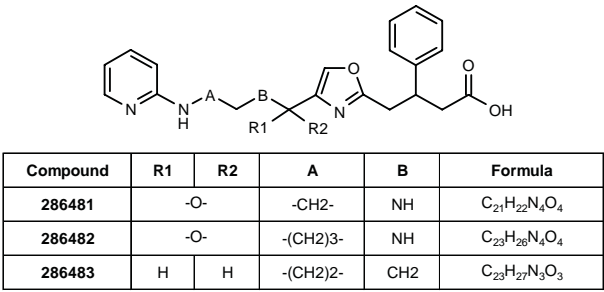
286479

(±)-3-Phenyl-4-[4-[*N*-[3-(2-pyridylamino)propyl]-carbamoyl]oxazol-2-yl]butyric acid



C₂₂ H₂₄ N₄ O₄; Mol wt: 408.4556

ACTION – An inhibitor of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin (vitronectin) receptors with selectivity relative to the gpIIb/IIIa (fibrinogen) receptor and potential in the treatment of inflammation, cancer, cardiovascular disorders such as atherosclerosis and restenosis, and osteoporosis. Other specifically claimed compounds from this series of oxazole derivatives include the following:



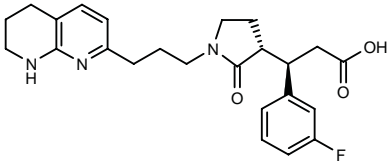
SOURCE – SmithKline Beecham.

REFERENCES

1. Manley, P.J. and Miller, W.H. (SmithKline Beecham Corp.) *Vitronectin receptor antagonists*. WO 0007544.

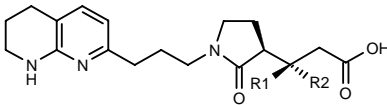
286516

3(R)-(3-Fluorophenyl)-3-[2-oxo-1-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]pyrrolidin-3(R)-yl]propionic acid

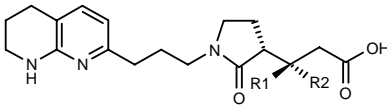


C24 H28 F N3 O3; Mol wt: 425.5012

ACTION – Integrin receptor antagonist, more particularly an integrin $\alpha_v\beta_3$, $\alpha_v\beta_5$ and/or $\alpha_v\beta_6$ receptor antagonist. Potentially useful for inhibiting bone resorption, treating and preventing osteoporosis and inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, inflammatory arthritis, viral disease, tumor growth and metastasis. Other specifically claimed compounds are:



Compound	R1	R2	Formula
286517	3-F-Ph	H	C ₂₄ H ₂₈ FN ₃ O ₃
286519	H	3-F-Ph	C ₂₄ H ₂₈ FN ₃ O ₃
286521	3-quinolyl	H	C ₂₇ H ₃₀ N ₄ O ₃
286524	H	3-quinolyl	C ₂₇ H ₃₀ N ₄ O ₃



Compound	R1	R2	Formula
286518	H	3-F-Ph	C ₂₄ H ₂₈ FN ₃ O ₃
286520	3-quinolyl	H	C ₂₇ H ₃₀ N ₄ O ₃
286523	H	3-quinolyl	C ₂₇ H ₃₀ N ₄ O ₃

SOURCE – Merck & Co.

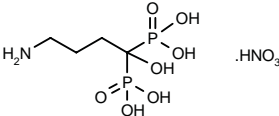
REFERENCES

1. Hutchinson, J.H. (Merck & Co., Inc.) *Integrin receptor antagonists*. WO 0009503.

ALENDRONATE NITRATE

285898

(4-Amino-1-hydroxybutylidene)bisphosphonic acid nitrate



C4 H13 N O7 P2 . H N O3; Mol wt: 312.1066

ACTION – Nitrate salt of alendronate for bone disorders, reported to possess improved therapeutic activity and gastrointestinal tolerability. When tested in rats, compound was shown to reduce aspirin-induced gastric damage by 4-5-fold compared to alendronate when both were given at a dose of 80 mg alendronate/kg p.o.

SOURCE – NicOx.

REFERENCES

1. Del Soldato, P. (NicOx SA) *Medicine nitrate salts*. WO 0006585.

DCR5

286748

Bone morphogenetic protein-binding protein

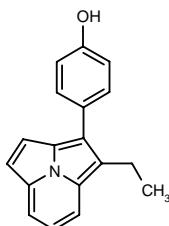
ACTION – Protein related to Gremlin, DAN (Differential-screening-selected gene Aberrative in Neuroblastoma) and Cerberus, with bone morphogenetic protein (BMP)-antagonist activity; specifically, it has been shown to selectively bind to BMP-2 and BMP-4 but not to BMP-5, BMP-11 or BMP-16. Also disclosed are nucleic acids encoding this protein and recombinant methods for its production. Potentially useful for regulating cartilage and bone growth.

SOURCE – Regeneron.

REFERENCES

1. Economides, A.N. and Stahl, N. (Regeneron Pharmaceuticals Inc.) *DCR5, a BMP-binding protein, and applications thereof*. WO 0011163.

NNC-45-0095

2860931-Ethyl-2-(4-hydroxyphenyl)pyrrolo[2,1,5-*cd*]indolizine4-(1-Ethylpyrrolo[2,1,5-*cd*]indolizin-2-yl)phenol

C18 H15 N O; Mol wt: 261.3225

M.p. 104-5 °C.

ACTION – High-affinity, nonsteroidal estrogen receptor ligand ($IC_{50} = 9.5$ nM) with full agonist activity, as demonstrated *in vitro* in a functional test in human endometrial adenocarcinoma cells, where it was able to stimulate alkaline phosphatase activity with an EC_{50} of 13 nM. *In vivo*, compound exhibited uterotrophic activity in both immature mice ($ED_{50} = 0.96$ nmol/g s.c.) and mature ovariectomized mice, and it was able to completely prevent bone loss induced by ovariectomy in mice after 5 weeks of daily treatment at 5 or 10 nmol/g s.c.

SOURCE – Novo Nordisk.

REFERENCES

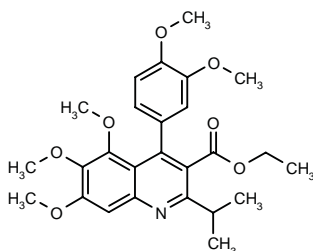
1. Jorgensen, A.S. et al. (Novo Nordisk A/S) *Pyrrolo[2,1,5-*cd*]indolizine derivs. useful in the prevention or treatment of estrogen related diseases or syndromes*. EP 0986560, WO 9855482.

2. Jorgensen, A.S. et al. *Synthesis and pharmacology of a novel pyrrolo[2,1,5-*cd*]indolizine (NNC 45-0095), a high affinity non-steroidal agonist for the estrogen receptor*. Bioorg Med Chem Lett 2000, 10(4): 399.

TREATMENT OF LIPOPROTEIN DISORDERS

285765

2-Isopropyl-4-(3,4-dimethoxyphenyl)-5,6,7-trimethoxyquinoline-3-carboxylic acid ethyl ester



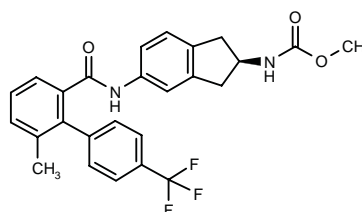
C26 H31 N O7; Mol wt: 469.5309

ACTION – Cholesterol-lowering agent, an inhibitor of the apical sodium codependent bile acid transporter (ASBT; $IC_{50} = 4.4$ μ M for inhibition of [14 C]-taurocholate uptake in baby hamster kidney cells transfected with cDNA of human ASBT). Potentially useful for the treatment of hyperlipidemia and to prevent arteriosclerosis and coronary heart disease.

SOURCE – Pharmacia.

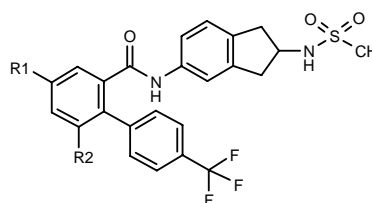
REFERENCES

1. Tollefson, M.B. et al. *A novel class of apical sodium co-dependent bile acid transporter inhibitors: The 2,3-disubstituted-4-phenylquinolines*. Bioorg Med Chem Lett 2000, 10(3): 277.

285807*N*-[5-[6-Methyl-4'-(trifluoromethyl)biphenyl-2-yl]carbox-amido]indan-2(*R*)-yl]carbamic acid methyl ester

C26 H23 F3 N2 O3; Mol wt: 468.4727

ACTION – An inhibitor of microsomal triglyceride transfer protein (MTP; $IC_{50} = 70$ nM) and apolipoprotein B (ApoB) secretion ($IC_{50} = 0.7$ nM in HepG2 cells), reported to lower plasma triglycerides and cholesterol *in vivo* at a dose of 10 mg/kg p.o. Potentially useful for the treatment and prevention of hyperlipidemia, hypercholesterolemia and hypertriglyceridemia and associated conditions, e.g., cardiovascular diseases including cardiac ischemia, atherosclerosis, obesity, pancreatitis and diabetes. Other compounds from this series of *N*-benzocycloalkyl-amide derivatives include the following:



Compound	R1	R2	Isomer	Formula
285808	H	Me	S	C ₂₅ H ₂₃ F ₃ N ₂ O ₃ S
285809	F	H	R	C ₂₄ H ₂₀ F ₄ N ₂ O ₃ S

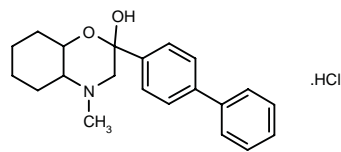
SOURCE – Novartis.

REFERENCES

1. Fink, C.A. et al. (Novartis AG) *N-Benzocycloalkyl-amide derivs. and their use as medicaments*. WO 0005201.

285822

2-(Biphenyl-4-yl)-4-methyloctahydro-2H-1,4-benzoxazin-2-ol hydrochloride



C21 H25 N O2 . HCl; Mol wt: 359.8944

White solid, m.p. 161-3 °C.

ACTION – Hypolipidemic agent and antioxidant proven to inhibit lipid peroxidation in rat hepatic microsomal membrane fractions with an IC₅₀ of 250 μM and to significantly reduce total (54%) and LDL cholesterol (51%) and triglyceride levels (49%) in plasma in hyperlipidemic rats at a dose of 28 μmol/kg i.p.

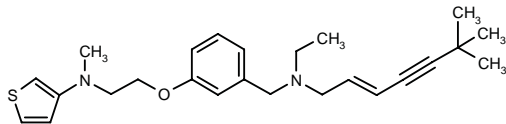
SOURCE – Aristotle University of Thessaloniki, Thessaloniki (GR).

REFERENCES

1. Chrysseilis, M.C. et al. *Hypocholesterolemic and hypolipidemic activity of some novel morpholine derivatives with antioxidant activity.* J Med Chem 2000, 43(4): 609.

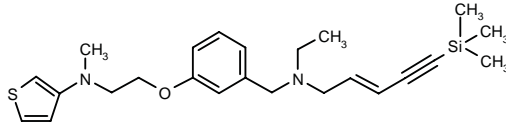
286097

N-[6,6-Dimethylhept-2(E)-en-4-ynyl]-N-ethyl-N-[3-[2-[N-methyl-N-(3-thienyl)amino]ethoxy]benzyl]amine



C25 H34 N2 O S; Mol wt: 410.6226

ACTION – Agent for the treatment of hypercholesterolemia, hyperlipidemia and arteriosclerosis, a squalene epoxidase inhibitor (IC₅₀ = 4.7 nM against enzyme from rat liver). Another compound from this series of benzylamine derivatives is:



286098: C24 H34 N2 O S Si

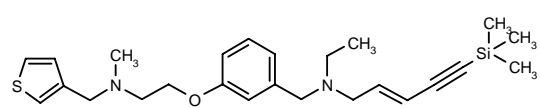
SOURCES – Tosoh; Welfide.

REFERENCES

1. Yamamoto, T. et al. (Tosoh Corporation;Yoshitomi Pharmaceutical Industries, Ltd.) *Novel benzylamine derivs. or their salts, and their preparation method.* JP 2000026456.

286099

N-Ethyl-N-[3-[2-[N-methyl-N-(3-thienylmethyl)amino]ethoxy]benzyl]-N-[5-(trimethylsilyl)pent-2(E)-en-4-ynyl]amine



C25 H36 N2 O S Si; Mol wt: 440.7244

ACTION – Agent for the treatment of hypercholesterolemia, hyperlipidemia and arteriosclerosis, a squalene epoxidase inhibitor (IC₅₀ = 4.57 nM against enzyme from rat liver). A representative compound from a series of benzylamine derivatives.

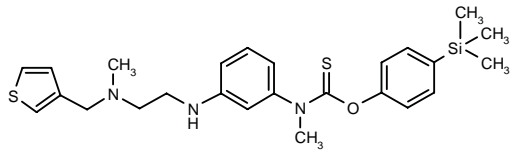
SOURCES – Tosoh; Welfide.

REFERENCES

1. Yamamoto, T. et al. (Tosoh Corporation;Yoshitomi Pharmaceutical Industries, Ltd.) *Novel benzylamine derivs. or their salts, and their preparation method.* JP 2000026476.

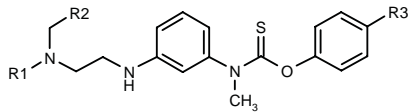
286100

N-Methyl-N-[3-[2-[N-methyl-N-(3-thienylmethyl)amino]ethylamino]phenyl]thiocarbamic acid O-[4-(trimethylsilyl)phenyl] ester



C25 H33 N3 O S2 Si; Mol wt: 483.7737

ACTION – Agent for the treatment of hypercholesterolemia, hyperlipidemia and arteriosclerosis, a squalene epoxidase inhibitor (IC₅₀ = 4.0 nM against enzyme from rat liver). Other compounds from this series of ethylene-diamine derivatives include the following:



Compound	R1	R2	R3	Formula
286101	3-thienyl-CH2	H	t-Bu	C ₂₆ H ₃₃ N ₃ OS ₂
286102	3-thienyl-CH2	Me	t-Bu	C ₂₇ H ₃₅ N ₃ OS ₂
286103	3-thienyl	H	Si(Me)3	C ₂₄ H ₃₁ N ₃ OS ₂ Si

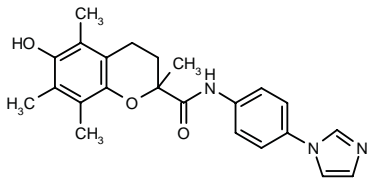
SOURCES – Tosoh; Welfide.

REFERENCES

1. Tokunaga, T. et al. (Tosoh Corporation;Yoshitomi Pharmaceutical Industries, Ltd.) *Novel ethylenediamine derivs.* JP 2000026452.

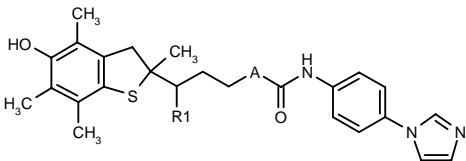
286244

6-Hydroxy-*N*-[4-(1*H*-imidazol-1-yl)phenyl]-2,5,7,8-tetra-methyl-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide



C23 H25 N3 O3; Mol wt: 391.4685

ACTION – Agent with lipid peroxidation-inhibitory and hypolipidemic activity that was shown to inhibit lipid peroxidation both *in vitro* in rat hepatic microsomes (IC₅₀ = 2.7 μM) and *in vivo* in CCl₄-treated rats (96% inhibition at a dose of 100 mg/kg p.o). In addition, when tested in hypercholesterolemic Syrian hamsters, compound gave 40 and 62% reductions in total cholesterol and triglycerides, respectively, at a dose of 25 mg/kg/day p.o. No toxicity was observed following repeated oral doses of 100 mg/kg/day x 7 days in rats. A representative compound from a series of phenylazole derivatives, wherein the following are also included:



Compound	R1	A	Formula
286245	Ph	-(CH2)3-	C ₃₄ H ₃₉ N ₃ O ₂ S
286246	H	-CH2-	C ₂₆ H ₃₁ N ₃ O ₂ S

SOURCE – Nippon Soda.

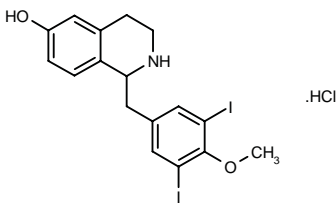
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1. Umeda, N. et al. (Nippon Soda Co., Ltd.) *Phenylazole cpds., process for producing the same and drugs for hyperlipemia*. WO 0006550.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

279920¹⁻⁴

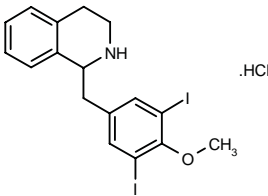
1-(3,5-Diiodo-4-methoxybenzyl)-1,2,3,4-tetrahydro-isoquinolin-6-ol hydrochloride



C17 H17 I2 N O2 . HCl; Mol wt: 557.5872

White crystals, *m.p.* 233-4 °C.

ACTION – Potent full agonist at human β₃-adrenoceptors with good selectivity over human β₂-adrenoceptors and inactive at human β₁-adrenoceptors. Potentially useful for the treatment of obesity and type II diabetes mellitus. Within this series of tetrahydroisoquinolines, the following is also included:



285819:^{1,3} C17 H17 I2 N O . HCl

SOURCE – Molecular Design International.

REFERENCES

1. Miller, D.D. and Feller, D.R. (Molecular Design International, Inc.) *β₃-Adrenoreceptor agonists, agonist compsns. and methods of using*. WO 9916752.

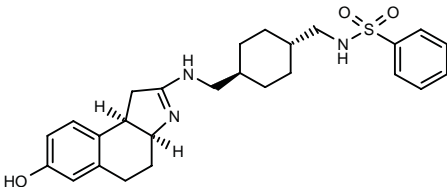
2. He, Y. et al. *Synthesis and human β-adrenoceptor activity of 1,2,3,4-tetrahydroisoquinoline-6-ol derivatives, in vitro*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 148.

3. He, Y. et al. *Synthesis and human β-adrenoceptor activity of 1-(3,5-diiodo-4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-6-ol derivatives in vitro*. J Med Chem 2000, 43(4): 591.

4. Nikulin, V.I. et al. *7-Substituted 1-aryl-1,2,3,4-tetrahydroisoquinoline-6-ols as selective agonists for human β₃-adrenoceptor*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 253.

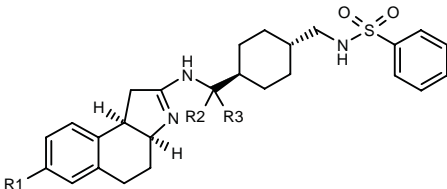
285745

N-[*trans*-4-(*cis*-7-Hydroxy-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indol-2-ylaminomethyl)cyclohexylmethyl]-benzenesulfonamide



C26 H33 N3 O3 S; Mol wt: 467.6307

ACTION – Neuropeptide Y (NPY) Y₅ receptor antagonist that binds to the human Y₅ receptor with nanomolar affinity (IC₅₀ = 1 nM) and inhibits the binding of labeled GTPγS in cells transfected with human Y₅ receptors in the presence of peptide YY. Potentially useful for the treatment of obesity and other eating disorders. Other related compounds are:



Compound	R1	R2	R3	Formula
285746	OH	-O-		C ₂₆ H ₃₁ N ₃ O ₄ S
285747	OMe	H	H	C ₂₇ H ₃₅ N ₃ O ₃ S
285748	H	-O-		C ₂₆ H ₃₁ N ₃ O ₃ S

SOURCE – R.W. Johnson.

REFERENCES

1. McNally, J.J. et al. *N-(Sulfonamido)alkyl[tetrahydro-1H-benzo[e]indol-2-yl]amines: Potent antagonists of human neuropeptide Y Y5 receptor*. Bioorg Med Chem Lett 2000, 10(3): 213.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

NESP

236400

Hyperglycosylated protein analogue of recombinant human erythropoietin (rhuEPO) produced by recombinant DNA technology in CHO cells. It is designed by substituting five amino acids in the primary sequence of rhuEPO to create two extra consensus N-linked glycosylation sites (Asn-X-Ser/Thr), resulting in five N-linked carbohydrate chains, a molecular weight of 38,000 Da and a carbohydrate content of 52%

Novel erythropoiesis-stimulating protein

ACTION – Agent for the treatment of anemia, a hyperglycosylated analogue of recombinant human erythropoietin (rhuEPO) shown to stimulate erythropoiesis in preclinical studies. Preliminary clinical trials demonstrated its efficacy and safety in the treatment of anemia in chronic renal failure patients. Compound exhibited a good pharmacokinetic profile after i.v. administration in dialysis patients, with a 3-fold longer serum half-life compared to rhuEPO, allowing less frequent dosing (once weekly). Currently undergoing phase III trials evaluating long-term efficacy and safety in the treatment of anemia in chronic renal failure.

SOURCES – Amgen; Kirin Brewery.

REFERENCES

1. Akahori, H. et al. *The effect of novel erythropoiesis stimulating protein (NESP) on anemia in a rat model of cisplatin-induced renal failure*. 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 847.

2. Akahori, H. et al. *The effect of novel erythropoiesis stimulating protein (NESP) on anemia induced by renal failure in rats*. Exp Hematol 1998, 26(8): 766.

3. Cooke, K. et al. *Novel erythropoiesis stimulating protein (NESP) alleviates anemia associated with chronic inflammatory disease in a rodent model*. 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 209.

4. Egrie, J.C. et al. *Novel erythropoiesis stimulating protein (NESP) has a longer serum half-life and greater in vivo biological activity than recombinant human erythropoietin (rHuEPO)*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 243.

5. Hartley, C. et al. *Pre-treatment with novel erythropoiesis stimulating protein (NESP) prevents chemotherapy induced anemia in mice*. 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 213.

6. Heatherington, A.C. et al. *Establishment of a PK-PD relationship for novel erythropoiesis stimulating protein (NESP) in dogs*. Annu Meet Am Assoc Pharm Sci (Nov 14-18, New Orleans) 1999, Abst 3762.

7. Macdougall, I.C. *Novel erythropoiesis stimulating protein (NESP) for the treatment of renal anemia*. J Am Soc Nephrol 1998, 9: Abst A1317.

8. Macdougall, I.C. et al. *Comparison of the pharmacokinetics of novel erythropoiesis stimulating protein (NESP) and epoetin alfa (rHEPO) in dialysis patients*. J Am Soc Nephrol 1997, 8: Abst A1233.

9. Macdougall, I.C. et al. *Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients*. J Am Soc Nephrol 1999, 10(11): 2392.

10. Vanreterghem, Y. et al. *Novel erythropoiesis stimulating protein (NESP) maintains hemoglobin (Hgb) in ESRD patients when administered once weekly or once every other week*. 32nd Annu Meet Am Soc Nephrol (Nov 5-8, Miami Beach) 1999, Abst A1365.

11. *Amgen announces 31 percent increase in earnings per share*. Amgen Inc. Press Release 1996, April 17.

12. *Amgen announces start of NESP clinical trials*. Amgen Inc. Press Release 1997, Jan 21.

13. *Amgen files for regulatory approval of NESP and Kineret during 1999*. DailyDrugNews.com (Daily Essentials) 2000, Jan 26.

14. *Amgen: Q1 1998 highlights*. DailyDrugNews.com (Daily Essentials) 1998, April 27.

15. *Amgen: Q2 1998 highlights*. DailyDrugNews.com (Daily Essentials) 1998, Aug 14.

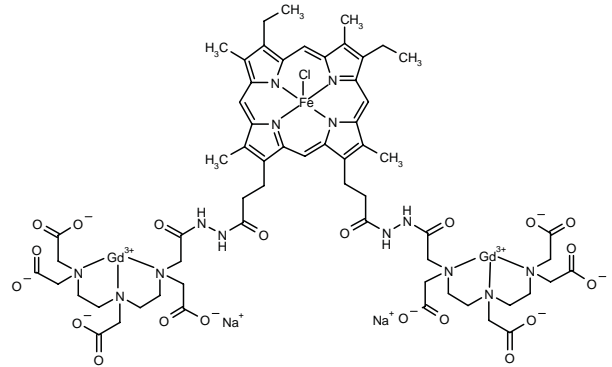
16. *Kirin Brewery starting clinical R&D in South East Asia: First of all TPO and then 3 new products in Taiwan*. Kagaku Kogyo Nippo 1996, September 25.

MONOGRAPH – Cases, A. *Novel Erythropoiesis Stimulating Protein*. Drugs Fut 2000, 25(3): 0246.

DIAGNOSTIC AGENTS

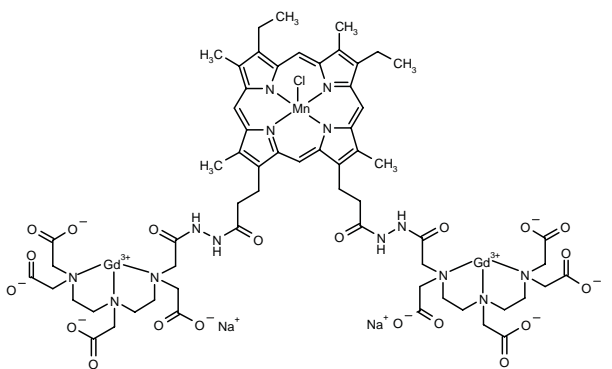
285812

(Chloro-3κCl)[μ₃-(7,12-diethyl-3,8,13,17-tetramethyl-21*H*,23*H*-porphyrin-3κ⁴*N*²¹,*N*²²,*N*²³,*N*²⁴)-2,18-diyl]bis[3,6,9-tris[(carboxy-1κO;2κO')methyl]-11-(oxo-1κO;2κO')-14-oxo-3,6,9,12,13-pentaaza-hexadecanoato-1κ⁴*N*³,*N*⁶,*N*⁹,*O*¹;2κ⁴*N*^{3'},*N*^{6'},*N*^{9'},*O*^{1'}](10-)]-3-iron-1,2-digadolinato(2-) disodium salt



C62 H74 Cl Fe Gd2 N14 Na2 O20; Mol wt: 1787.1230

ACTION – Paramagnetic 3,8-substituted porphyrin derivative reported to exhibit high relaxivity, good aqueous solubility and high stability both *in vitro* and *in vivo*, potentially useful in the magnetic resonance imaging (MRI) of necrosis and infarction. Another exemplified compound is:



285813: C62 H74 Cl Gd2 Mn N14 Na2 O20

SOURCE – R.W. Johnson.

REFERENCES

1. McNally, J.J. et al. *N*-(Sulfonamido)alkyl[tetrahydro-1*H*-benzo[*e*]indol-2-yl]amines: Potent antagonists of human neuropeptide Y Y5 receptor. *Bioorg Med Chem Lett* 2000, 10(3): 213.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

NESP

236400

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2. Akahori, H. et al. *The effect of novel erythropoiesis stimulating protein (NESP) on anemia induced by renal failure in rats.* *Exp Hematol* 1998, 26(8): 766.

3. Cooke, K. et al. *Novel erythropoiesis stimulating protein (NESP) alleviates anemia associated with chronic inflammatory disease in a rodent model.* 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 209.

4. Egrie, J.C. et al. *Novel erythropoiesis stimulating protein (NESP) has a longer serum half-life and greater in vivo biological activity than recombinant human erythropoietin (rHuEPO).* *Blood* 1997, 90(10, Suppl. 1, Part 1): Abst 243.

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6. Heatherington, A.C. et al. *Establishment of a PK-PD relationship for novel erythropoiesis stimulating protein (NESP) in dogs.* Annu Meet Am Assoc Pharm Sci (Nov 14-18, New Orleans) 1999, Abst 3762.

7. Macdougall, I.C. *Novel erythropoiesis stimulating protein (NESP) for the treatment of renal anemia.* *J Am Soc Nephrol* 1998, 9: Abst A1317.

8. Macdougall, I.C. et al. *Comparison of the pharmacokinetics of novel erythropoiesis stimulating protein (NESP) and epoetin alfa (rHEPO) in dialysis patients.* *J Am Soc Nephrol* 1997, 8: Abst A1233.

9. Macdougall, I.C. et al. *Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients.* *J Am Soc Nephrol* 1999, 10(11): 2392.

10. Vanreterghem, Y. et al. *Novel erythropoiesis stimulating protein (NESP) maintains hemoglobin (Hgb) in ESRD patients when administered once weekly or once every other week.* 32nd Annu Meet Am Soc Nephrol (Nov 5-8, Miami Beach) 1999, Abst A1365.

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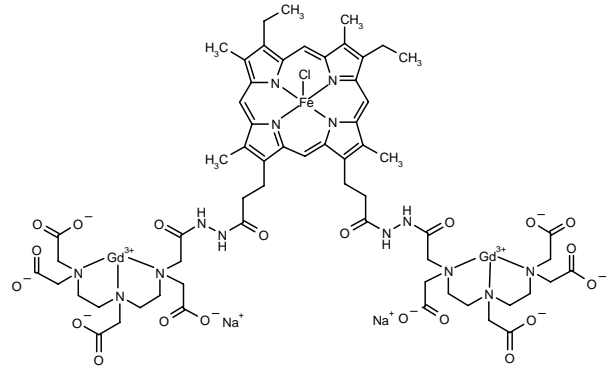
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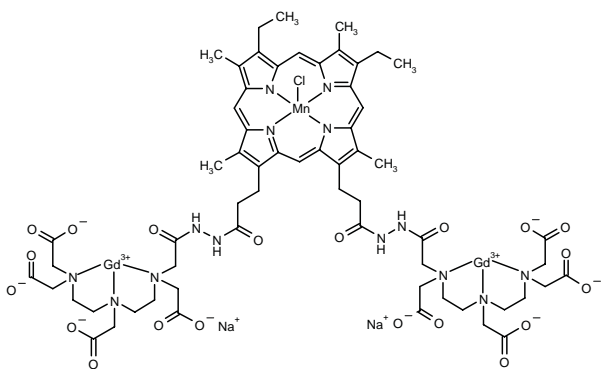
285812

(Chloro-3κCl)[μ₃-(7,12-diethyl-3,8,13,17-tetramethyl-21*H*,23*H*-porphyrin-3κ⁴*N*²¹,*N*²²,*N*²³,*N*²⁴)-2,18-diyl]bis[3,6,9-tris[(carboxy-1κO;2κO')methyl]-11-(oxo-1κO;2κO')-14-oxo-3,6,9,12,13-pentaaza-hexadecanoato-1κ⁴*N*³,*N*⁶,*N*⁹,*O*¹;2κ⁴*N*^{3'},*N*^{6'},*N*^{9'},*O*^{1'}](10-)]-3-iron-1,2-digadolinato(2-) disodium salt



C62 H74 Cl Fe Gd2 N14 Na2 O20; Mol wt: 1787.1230

ACTION – Paramagnetic 3,8-substituted porphyrin derivative reported to exhibit high relaxivity, good aqueous solubility and high stability both *in vitro* and *in vivo*, potentially useful in the magnetic resonance imaging (MRI) of necrosis and infarction. Another exemplified compound is:



285813: C62 H74 Cl Gd2 Mn N14 Na2 O20

SOURCE – Schering AG.

REFERENCES

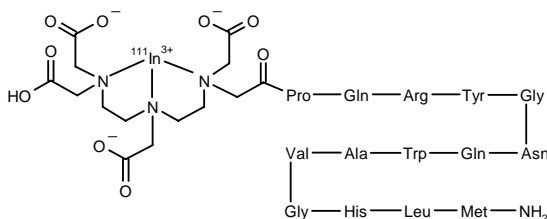
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[¹¹¹In-DTPA-Pro¹,Tyr⁴]-BOMBESIN

284011

[N-[2-[[2-[Bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl-L-prolyl-L-glutamyl-L-arginyl-L-tyrosylglycyl-L-asparagyl-L-glutamyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-L-leucyl-L-methionamidato(3-)]indium-¹¹¹In

[¹¹¹In-DTPA-Pro¹,Tyr⁴]-BN



C88 H128 N27 O27 S . In; Mol wt: 2139.2070

ACTION – High-affinity bombesin receptor ligand (IC₅₀ = 8 nM against [¹²⁵I-Tyr]-bombesin binding in rat pituitary tumor cell membranes) with functional agonist activity, as demonstrated by its ability to stimulate prolactin secretion from rat pituitary tumor cells. Rat biodistribution studies with ¹¹¹In-radiolabeled compound showed high specific uptake in gastrointestinal tract tissues, notably in pancreas and kidneys, with rapid clearance of radioactivity from the blood compartment. In rats bearing bombesin receptor-positive tumors such as pancreas CA20948 and colon CC531 carcinomas, specific uptake of the radiolabeled compound was found. Potentially useful as a radioligand for scintigraphy of bombesin receptor-expressing tumors.

SOURCE – Mallinckrodt.

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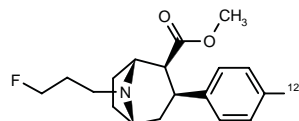
IOFLUPANE (¹²³I)

Prop INN

273559

(1*R*,2*S*,3*S*,5*S*)-8-(3-Fluoropropyl)-3-(4-[¹²³I]iodophenyl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester

β-CIT-FP
DaTSCANTM



C18 H23 F I N O2; Mol wt: 427.3827

M.p. 82-3 °C.

ACTION – Imaging agent for the diagnosis of Parkinson's disease and related syndromes such as essential tremor, an iodine-labeled agent that binds to dopamine transporters on neurons (K_i = 3.5 nM for the unlabeled compound). Biodistribution studies in rats with iodinated compound demonstrated high accumulation of radioactivity in striatum and less in brain areas with high densities of 5-HT uptake sites. Clinical studies demonstrated that the compound is a suitable radiotracer for imaging dopamine transporters in the living human brain. It recently received a positive opinion from the scientific advisory panel for the European Medicines Evaluation Agency (EMA).

SOURCE – Nycomed Amersham.

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4. Bergstrom, K.A. et al. *Characterization of C-11 or I-123 labelled β-CIT-FP and β-CIT-FE metabolism measured in monkey and human plasma. Identification of two labelled metabolites with HPLC*. Hum Psychopharmacol 1996, 11(6): 483.
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16. Seibyl, J.P. et al. *Iodine-123-β-CIT and iodine-123 FPCIT SPECT measurement of dopamine transporters in healthy subjects and Parkinson's patients.* J Nucl Med 1998, 39(9): 1500.

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22. Tissingh, G. et al. *Nigrostriatal dopaminergic imaging with iodine-123-β CIT-FP/SPECT and fluorine-18-FDOPA/PET.* J Nucl Med 1997, 38(8): 1271.

23. Walker, Z. et al. *In vivo demonstration of dopaminergic degeneration in dementia with Lewy bodies.* Lancet 1999, 354(9179): 646.

24. *DaTSCAN recieves positive opinion from the CPMP.* DailyDrugNews.com (Daily Essentials) 2000, March 28.

25. *Nycomed Amersham files for approval of novel PD diagnostic.* DailyDrugNews.com (Daily Essentials) 1998, Dec 11.

26. *Nycomed Amersham highlights product development efforts for year-end 1999.* DailyDrugNews.com (Daily Essentials) 2000, March 10.

27. *Nycomed Amersham: Nine-month highlights.* DailyDrugNews.com (Daily Essentials) 1998, April 15.

28. *Nycomed Amersham: Six month highlights.* DailyDrugNews.com (Daily Essentials) 1998, Sept 18.

29. *Proposed international nonproprietary names (Prop. INN): List 75.* WHO Drug Inf 1996, 10(2): 102.

PHARMACOLOGICAL TOOLS

285764

L-Cysteinyl-L-arginyl-L-alanyl-L-leucyl-L-leucyl-L-arginylglycyl-L-alanyl-L-prolyl-L-phenylalanyl-L-histidyl-L-leucyl-L-alanyl-L-glutamyl-L-cysteine

C72 H117 N23 O18 S2; Mol wt: 1656.9910

ACTION – Peptide with affinity for the human fibroblast growth factor (FGF) receptor, with an amino acid sequence unrelated to native human FGF.

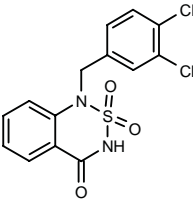
SOURCE – Chugai.

REFERENCES

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285835

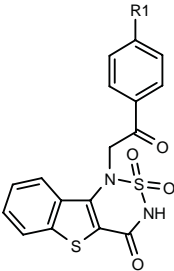
1-(3,4-Dichlorobenzyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazin-4-one *S,S*-dioxide



C14 H10 Cl2 N2 O3 S; Mol wt: 357.2160

White solid, m.p. 250-2 °C.

ACTION – Phosphodiesterase type 7 (PDE7) inhibitor (IC₅₀ = 8 μM) with a trend toward selectivity over PDE3 and PDE4 (IC₅₀ = 24 and 19 μM, respectively). Considered a lead compound for further chemical optimization to develop highly selective PDE7 inhibitors. Other benzyl derivatives of 2,1,3-benzo- and benzothieno[3,2-*a*]-thiadiazine 2,2-dioxides are:



Compound	R1	Formula
285833	OMe	C ₁₈ H ₁₄ N ₂ O ₅ S ₂
285834	Ph	C ₂₃ H ₁₆ N ₂ O ₄ S ₂

Selective PDE7 inhibitors may be useful for the treatment of T-cell-related disorders, or simply as tools for elucidating the functional role of this cAMP-specific PDE.

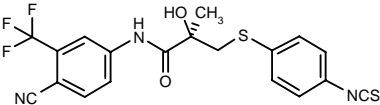
SOURCES – Almirall Prodesfarma; CSIC, Madrid (ES).

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285816

***N*-[4-Cyano-3-(trifluoromethyl)phenyl]-2(*R*)-hydroxy-2-methyl-3-[4-(isothiocyanato)phenylsulfanyl]propionamide**



C19 H14 F3 N3 O2 S2; Mol wt: 437.4646

Light yellow solid, m.p. 129-30 °C; [α]_D²⁷ +54.9° (c 2, acetone).

13. Lavalaye, J. et al. [¹²³I]FP-CIT binding in rat brain after acute and sub-chronic administration of dopaminergic medication. *Eur J Nucl Med* 2000, 27(3): 346.

14. Neumeyer, J.L. et al. N-ω-Fluoroalkyl analogs of (1*R*)-2β-carbomethoxy-3β-(4-iodophenyl)-tropane (β-CIT): Radiotracers for positron emission tomography and single photon emission computed tomography imaging of dopamine transporters. *J Med Chem* 1994, 37(11): 1558.

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PHARMACOLOGICAL TOOLS

285764

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C72 H117 N23 O18 S2; Mol wt: 1656.9910

ACTION – Peptide with affinity for the human fibroblast growth factor (FGF) receptor, with an amino acid sequence unrelated to native human FGF.

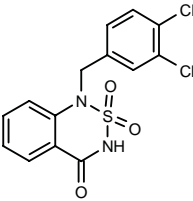
SOURCE – Chugai.

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285835

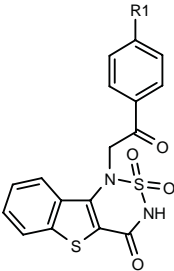
1-(3,4-Dichlorobenzyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazin-4-one S,S-dioxide



C14 H10 Cl2 N2 O3 S; Mol wt: 357.2160

White solid, m.p. 250-2 °C.

ACTION – Phosphodiesterase type 7 (PDE7) inhibitor (IC₅₀ = 8 μM) with a trend toward selectivity over PDE3 and PDE4 (IC₅₀ = 24 and 19 μM, respectively). Considered a lead compound for further chemical optimization to develop highly selective PDE7 inhibitors. Other benzyl derivatives of 2,1,3-benzo- and benzothieno[3,2-*a*]-thiadiazine 2,2-dioxides are:



Compound	R1	Formula
285833	OMe	C ₁₈ H ₁₄ N ₂ O ₅ S ₂
285834	Ph	C ₂₃ H ₁₆ N ₂ O ₄ S ₂

Selective PDE7 inhibitors may be useful for the treatment of T-cell-related disorders, or simply as tools for elucidating the functional role of this cAMP-specific PDE.

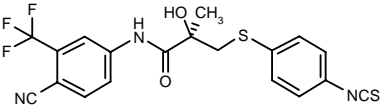
SOURCES – Almirall Prodesfarma; CSIC, Madrid (ES).

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285816

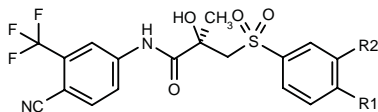
N-[4-Cyano-3-(trifluoromethyl)phenyl]-2(*R*)-hydroxy-2-methyl-3-[4-(isothiocyanato)phenylsulfanyl]propionamide



C19 H14 F3 N3 O2 S2; Mol wt: 437.4646

Light yellow solid, m.p. 129-30 °C; [α]_D²⁷ +54.9° (c 2, acetone).

ACTION – High-affinity, nonsteroidal androgen receptor (AR) ligand ($K_i = 0.6$ nM) derived from structural modifications of bicalutamide; the compound is the first specific chemoaffinity ligand for the AR and binds irreversibly to the receptor. Potentially useful as a tool for the molecular characterization of the ligand-binding domain of the AR. Other related isothiocyanate compounds are:



Compound	R1	R2	Formula
285817	-NCS	H	C ₁₉ H ₁₄ F ₃ N ₃ O ₄ S ₂
285818	H	-NCS	C ₁₉ H ₁₄ F ₃ N ₃ O ₄ S ₂

SOURCE – University of Tennessee, Memphis, TN (US).

REFERENCES

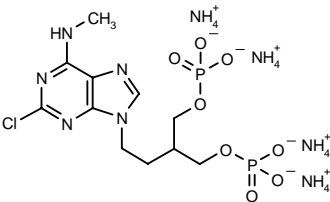
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MRS-2286

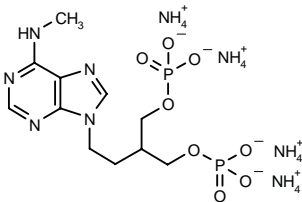
285839

2-[2-[2-Chloro-6-(methylamino)purin-9-yl)ethyl]propane-1,3-diol bis(monophosphate) tetraammonium salt



C11 H14 Cl N5 O8 P2 . 4 H4 N; Mol wt: 513.8140

ACTION – Purine P2Y₁ receptor antagonist, a nucleotide analogue proven to inhibit 2-MeSADP-induced phospholipase C stimulation in turkey erythrocyte membranes ($IC_{50} = 0.84$ μM) while exerting no agonist activity at this receptor and no agonist or antagonist activity at rat P2X₁ receptors. Potentially useful as a pharmacological probe for P2 receptor function in platelets and other systems. Another compound within this series of acyclic analogues of deoxyadenosine 3',5'-biphosphates is:



MRS-2277 [285838]: C11 H15 N5 O8 P2 . 4 H4 N

SOURCES – Universidad de Buenos Aires, Buenos Aires (AR); National Institutes of Health, Bethesda, MD (US); University of North Carolina, Chapel Hill, NC (US).

REFERENCES

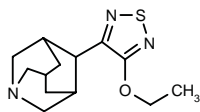
1. Kim, Y.-C. et al. *Acyclic analogues of deoxyadenosine 3',5'-bisphosphates as P2Y1 receptor antagonists.* J Med Chem 2000, 43(4): 746.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

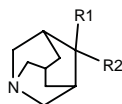
286782

4-(4-Ethoxy-1,2,5-thiadiazol-3-yl)-1-azaadamantane



C13 H19 N3 O S; Mol wt: 265.3791

ACTION – Analgesic agent that acts as a selective agonist at central muscarinic M₄ receptors. Compound was found to bind to the agonist binding site of cloned human M₄ receptors in CHO-K1 cells with an affinity of 0.46 nM. In addition, it was found to be effective in the tail-flick assay in mice (ED₅₀ = 1.5 mg/kg i.v.), with little or no salivation, sedation and hypothermia being seen at the ED₅₀ dose. In addition to pain, compound is also expected to have utility in the treatment of schizophrenia and cognitive disorders such as Alzheimer's disease. Other specifically claimed compounds from this series of azaadamantanes, azanoradamantanes and azahomoadamantanes useful as muscarinic agonists and antagonists include the following:



Compound	R1	R2	Formula
286783	-C(CN)(CO2Et)-		C ₁₄ H ₁₈ N ₂ O ₂
286784	CH(CN)CO2Et	H	C ₁₄ H ₂₀ N ₂ O ₂
286785	4-Cl-1,2,5-thiadiazol-3-yl	Cl	C ₁₁ H ₁₃ Cl ₂ N ₃ S
286786	4-Cl-1,2,5-thiadiazol-3-yl	H	C ₁₁ H ₁₄ ClN ₃ S
286787	4-MeO-1,2,5-thiadiazol-3-yl	H	C ₁₂ H ₁₇ N ₃ OS
286788	4-PrO-1,2,5-thiadiazol-3-yl	H	C ₁₄ H ₂₁ N ₃ OS
286789	4-BuO-1,2,5-thiadiazol-3-yl	H	C ₁₅ H ₂₃ N ₃ OS
286790	4-(cyclopropyl-CH2O)- -1,2,5-thiadiazol-3-yl	H	C ₁₅ H ₂₁ N ₃ OS
286791	4-i-BuO-1,2,5-thiadiazol-3-yl	H	C ₁₆ H ₂₃ N ₃ OS

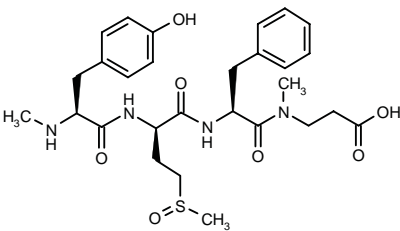
SOURCE – UCB.

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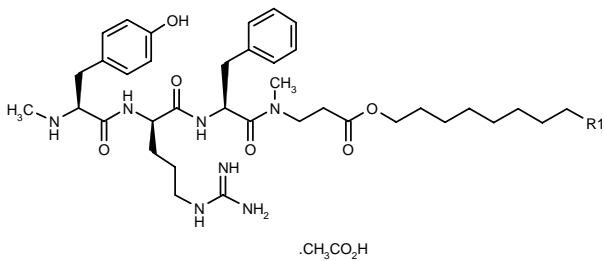
287099

N-Methyl-L-tyrosyl-(S-oxido)-D-methionyl-L-phenylalanyl-
(N-methyl)-β-alanine



C28 H38 N4 O7 S; Mol wt: 574.6952

ACTION – Analgesic agent whose activity was evaluated in the mouse tail pressure test (ED₅₀ = 1.20 mg/kg s.c., 27.8 mg/kg p.o.). Other compounds within this series of peptide derivatives include the following:



Compound	R1	Formula
287100	H	C ₃₇ H ₅₇ N ₇ O ₆ .C ₂ H ₄ O ₂
287101	Et	C ₃₉ H ₆₁ N ₇ O ₆ .C ₂ H ₄ O ₂

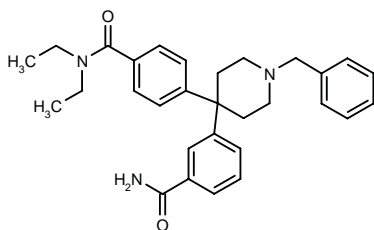
SOURCE – Fuji Chemical.

REFERENCES

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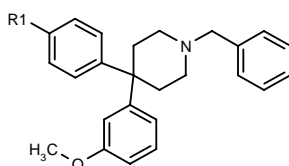
287293

4-[1-Benzyl-4-[3-(carbamoyl)phenyl]piperidin-4-yl]-N,N-diethylbenzamide



C30 H35 N3 O2; Mol wt: 469.6255

ACTION – Potent and selective δ -opioid receptor ligand, potentially useful for the treatment of pain, as well as neurological, gastrointestinal, inflammatory and immune disorders. Other exemplified compounds from this series of 4,4-biaryl piperidine derivatives include the following:



Compound	R1	Formula
287294	2-thienyl	C ₂₉ H ₂₉ NOS
287295	CN	C ₂₆ H ₂₆ N ₂ O
287296	5-tetrazolyl	C ₂₆ H ₂₇ N ₅ O
287297	4,4-(Me)2-4,5-dihydro-2-oxazolyl	C ₃₀ H ₃₄ N ₂ O ₂
287298	CH(Me)2OH	C ₂₈ H ₃₃ NO ₂
287299	CONHNH2	C ₂₆ H ₂₉ N ₃ O ₂
287300	cyclobutyl-CONHNHCO	C ₃₁ H ₃₅ N ₃ O ₃
287301	5-cyclobutyl-1,3,4-oxadiazol-2-yl	C ₃₁ H ₃₃ N ₃ O ₂

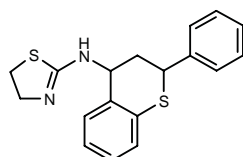
SOURCE – Pfizer.

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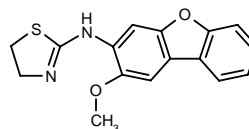
287521¹

N-(4,5-Dihydrothiazol-2-yl)-N-(2-phenyl-3,4-dihydro-2H-1-benzothiopyran-4-yl)amine



C18 H18 N2 S2; Mol wt: 326.4862

ACTION – Potent and selective α_{2C} -adrenoceptor agonist (EC_{50} = 0.1 nM for elevating cAMP levels in CHO cells transfected with cloned human receptors) with > 100,000-fold selectivity over α_{2A} -adrenoceptors. Potentially useful for the treatment of pain. Another related compound is:



287522²: C16 H14 N2 O2 S

SOURCE – AstraZeneca.

REFERENCES

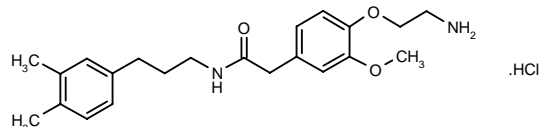
1. Bare, T.M. et al. Selective α_{2C} -adrenoceptor agonist activity of imidazole, imidazoline, and imidazoline-related derivatives. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MED1 268.
2. Murphy, M. et al. Design, synthesis, and $\alpha_{2A/2C}$ adrenoceptor agonist activity of biphenyl-imidazoline and thiazoline analogs. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MED1 269.

DA-5018

246619

2-[4-(2-Aminoethoxy)-3-methoxyphenyl]-N-[3-(3,4-dimethylphenyl)propyl]acetamide hydrochloride

KR-25018



C22 H30 N2 O3 . HCl; Mol wt: 406.9509

ACTION – Nonopioid analgesic agent, a capsaicin derivative with improved potency, therapeutic range and oral availability. The analgesic effects of compound were mediated by the vanilloid-sensitive neural pathway and by direct binding to the vanilloid receptor. In preclinical experiments orally administered compound exhibited potent analgesic activity in the phenylbenzoquinone-induced writhing test in mice, the adjuvant arthritis flexion test in rats and the tail-flick test in mice, where it was as potent as morphine. In addition, a cream formulation exhibited antipruritic effects in two models of itching in mice.

SOURCES – Dong-A; Korea Research Institute of Chemical Technology, Taejeon (KR); Stiefel.

REFERENCES

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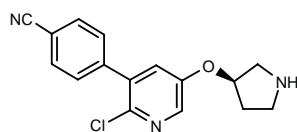
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RWJ-314313

287033

4-[2-Chloro-5-[3(*R*)-pyrrolidinyloxy]pyridin-3-yl]benzonitrile



C₁₆ H₁₄ Cl N₃ O; Mol wt: 299.7596

ACTION – Neuronal nicotinic acetylcholine receptor ligand with nanomolar affinity for the $\alpha 4\beta 2$ subtype (IC_{50} = 22 nM). Potentially useful as an analgesic agent.

SOURCE – R.W. Johnson.

REFERENCES

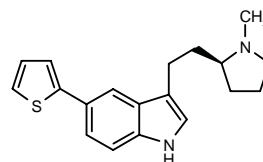
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ANTIMIGRAINE DRUGS

ALX-0388²

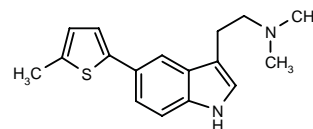
287073

3-[2-[1-Methylpyrrolidin-2(*R*)-yl]ethyl]-5-(2-thienyl)-1*H*-indole



C₁₉ H₂₂ N₂ S; Mol wt: 310.4628

ACTION – 5-HT_{1D} receptor agonist with high affinity for this receptor (K_i = 2.4 nM) and over 30-fold selectivity versus 5-HT_{1B} receptors (K_i = 75 nM). Potentially useful for the treatment of headache recurrence associated with migraine. Another 5-thienyltryptamine derivative is:



ALX-0501 [260022]*^{1,2}: C₁₇ H₂₀ N₂ S

SOURCE – NPS Allelix.

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*Identified compound **260022** (see **258995**) Drug Data Rep 1998, 020(03): 0198.

ANESTHETIC DRUGS

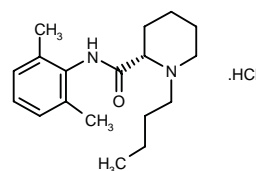
LEVOBUPIVACAINE⁺ HYDROCHLORIDE

Prop INN; USAN; BANM

220671

(–)-(S)-1-Butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide hydrochloride

(–)-Bupivacaine hydrochloride



C₁₈ H₂₈ N₂ O . HCl; Mol wt: 324.8931

ACTION – Long-acting, highly potent local anesthetic, a single enantiomer of bupivacaine hydrochloride.

INDICATION – Production of local or regional anesthesia for surgery and obstetrics and for postoperative pain management.

PRESENTATION – Single-use vials (10 and 30 ml) of a solution containing levobupivacaine hydrochloride equiv. to 2.5, 5.0 and 7.5 mg/ml levobupivacaine.

PROPRIETARY NAME – *Chirocaine* (US).

SOURCES – Celltech Group; marketed by Purdue Pharma.

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*Drug Data Rep 1995, 017(06): 0504.

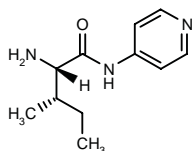
ADJUNCTS TO ANESTHESIA

LI-8

286270

L-Isoleucyl-4-aminopyridine

2(S)-Amino-3(S)-methyl-N-(4-pyridyl)pentanamide



C11 H17 N3 O; Mol wt: 207.2753

ACTION – Stable 4-aminopyridine derivative with the ability to enhance electrically stimulated acetylcholine release in rat cerebral cortex slices, while having no effect against acetylcholinesterase or butyrylcholinesterase and exhibiting few side effects. Considered a promising clinical candidate for reversing residual neuromuscular block.

SOURCE – Albert Einstein College of Medicine, New York, NY (US).

REFERENCES

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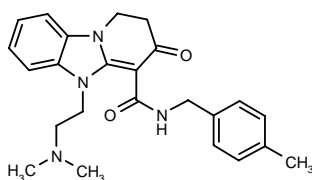
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PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

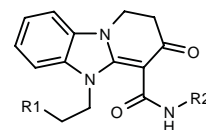
286697

5-[2-(Dimethylamino)ethyl]-N-(4-methylbenzyl)-3-oxo-1,2,3,5-tetrahydropyrido[1,2-a]benzimidazole-4-carboxamide



C24 H28 N4 O2; Mol wt: 404.5112

ACTION – Agent for the treatment of anxiety, Down's syndrome, depression, sleep, cognitive and seizure disorders, overdose with benzodiazepine drugs and for enhancing alertness, with high and selective affinity for the benzodiazepine binding site on the GABA_A receptor complex. Other specifically claimed compounds from this series of oxo-pyridoimidazole-carboxamides include the following:



Compound	R1	R2	Formula
286700	N(Me)2	CH2Ph	C ₂₃ H ₂₆ N ₄ O ₂
286703	CH2N(Me)2	CH2Ph	C ₂₄ H ₂₈ N ₄ O ₂
286705	H	4-(EtNHCH2CH2O)-Ph	C ₂₄ H ₂₈ N ₄ O ₃
286706	H	4-[2(S)-pyrrolidinyl-CH2O]-Ph	C ₂₅ H ₂₈ N ₄ O ₃
286707	H	3-F-4-[2(R)-pyrrolidinyl-CH2O]-Ph	C ₂₅ H ₂₇ FN ₄ O ₃
286708	OEt	4-(EtNHCH2CH2O)-Ph	C ₂₆ H ₃₂ N ₄ O ₄
286709	H	4-(4-morpholinyl-CH2-CH2NHCH2CH2O)-PhCH2	C ₂₉ H ₃₇ N ₅ O ₄

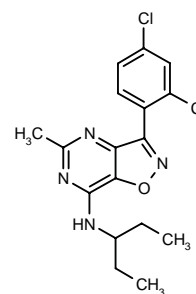
SOURCE – Neurogen.

REFERENCES

1. Rachwal, B. et al. (Neurogen Corp.) *Oxo-pyridoimidazole-carboxamides: GABA brain receptor ligands*. WO 0010973.

286763

N-[3-(2,4-Dichlorophenyl)-5-methylisoxazolo[4,5-d]pyrimidin-7-yl]-N-(1-ethylpropyl)amine



C17 H18 Cl2 N4 O; Mol wt: 365.2622

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist with potential for the treatment of psychiatric and neurological disorders including affective disorder, anxiety, depression, headache, irritable bowel syndrome, posttraumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa and other eating disorders, drug addiction and withdrawal, inflammatory diseases, cardiovascular and fertility disorders, HIV infection, obesity, head and spinal cord trauma, epilepsy, stroke, amyotrophic lateral sclerosis and hypoglycemia. A representative compound from a series of isoxazolo[4,5-d]pyrimidine derivatives.

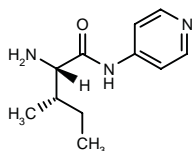
ADJUNCTS TO ANESTHESIA

LI-8

286270

L-Isoleucyl-4-aminopyridine

2(S)-Amino-3(S)-methyl-N-(4-pyridyl)pentanamide



C11 H17 N3 O; Mol wt: 207.2753

ACTION – Stable 4-aminopyridine derivative with the ability to enhance electrically stimulated acetylcholine release in rat cerebral cortex slices, while having no effect against acetylcholinesterase or butyrylcholinesterase and exhibiting few side effects. Considered a promising clinical candidate for reversing residual neuromuscular block.

SOURCE – Albert Einstein College of Medicine, New York, NY (US).

REFERENCES

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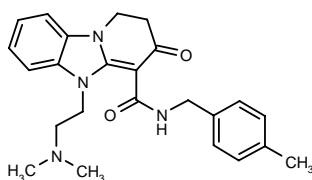
1. Nagashima, H. et al. *The effect of a 4-aminopyridine (4-AP) derivative, LI-8, on acetylcholine (ACH) release from cerebral cortex of the rat and on human cholinesterase (CHE) activity*. *Anesth Analg* 2000, 90(2, Suppl. S): Abst S-448.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

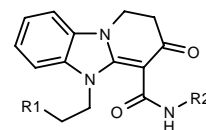
286697

5-[2-(Dimethylamino)ethyl]-N-(4-methylbenzyl)-3-oxo-1,2,3,5-tetrahydropyrido[1,2-a]benzimidazole-4-carboxamide



C24 H28 N4 O2; Mol wt: 404.5112

ACTION – Agent for the treatment of anxiety, Down's syndrome, depression, sleep, cognitive and seizure disorders, overdose with benzodiazepine drugs and for enhancing alertness, with high and selective affinity for the benzodiazepine binding site on the GABA_A receptor complex. Other specifically claimed compounds from this series of oxo-pyridoimidazole-carboxamides include the following:



Compound	R1	R2	Formula
286700	N(Me)2	CH2Ph	C ₂₃ H ₂₆ N ₄ O ₂
286703	CH2N(Me)2	CH2Ph	C ₂₄ H ₂₈ N ₄ O ₂
286705	H	4-(EtNHCH2CH2O)-Ph	C ₂₄ H ₂₈ N ₄ O ₃
286706	H	4-[2(S)-pyrrolidinyl-CH2O]-Ph	C ₂₅ H ₂₈ N ₄ O ₃
286707	H	3-F-4-[2(R)-pyrrolidinyl-CH2O]-Ph	C ₂₅ H ₂₇ FN ₄ O ₃
286708	OEt	4-(EtNHCH2CH2O)-Ph	C ₂₆ H ₃₂ N ₄ O ₄
286709	H	4-(4-morpholinyl-CH2-CH2NHCH2CH2O)-PhCH2	C ₂₉ H ₃₇ N ₅ O ₄

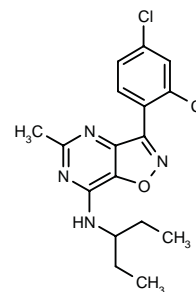
SOURCE – Neurogen.

REFERENCES

1. Rachwal, B. et al. (Neurogen Corp.) *Oxo-pyridoimidazole-carboxamides: GABA brain receptor ligands*. WO 0010973.

286763

N-[3-(2,4-Dichlorophenyl)-5-methylisoxazolo[4,5-d]pyrimidin-7-yl]-N-(1-ethylpropyl)amine



C17 H18 Cl2 N4 O; Mol wt: 365.2622

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist with potential for the treatment of psychiatric and neurological disorders including affective disorder, anxiety, depression, headache, irritable bowel syndrome, posttraumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa and other eating disorders, drug addiction and withdrawal, inflammatory diseases, cardiovascular and fertility disorders, HIV infection, obesity, head and spinal cord trauma, epilepsy, stroke, amyotrophic lateral sclerosis and hypoglycemia. A representative compound from a series of isoxazolo[4,5-d]pyrimidine derivatives.

SOURCE – DuPont Pharmaceuticals.

REFERENCES

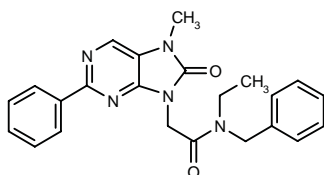
1. Frieze, W.E. (DuPont Pharmaceuticals Co.) *Isoxazolo[4,5-d]pyrimidines as CRF antagonists*. WO 0011003.

AC-5216

287245

N-Benzyl-*N*-ethyl-2-(7-methyl-8-oxo-2-phenyl-7,8-dihydro-9*H*-purin-9-yl)acetamide

SX-5216



C23 H23 N5 O2; Mol wt: 401.4677

ACTION – Anxiolytic agent, a selective ligand for the mitochondrial benzodiazepine receptor ($IC_{50} = 0.85$ nM) with high selectivity over type I and type II central benzodiazepine binding sites ($IC_{50} > 1$ μ M). Compound exhibited strong anxiolytic activity in animal models including the mouse light–dark box test, the Vogel conflict test in rats, the social interaction test in mice and the communication box test in mice (minimum effective dose [MED] = 0.003, 0.3, 0.01 and 10 mg/kg p.o., respectively). Despite its strong anxiolytic activity, compound lacked classical side effects of central benzodiazepine agonists such as muscle relaxation, amnesia and potentiation of anesthesia (MED or $ED_{50} > 100$ mg/kg p.o.).

SOURCE – Dainippon Pharmaceutical.

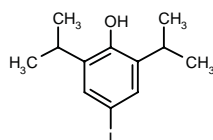
REFERENCES

1. Murata, T. et al. (Dainippon Pharmaceutical Co., Ltd.) *2-Aryl-8-oxodihydropurine derivs., process for producing the same, medicinal compns. containing the same, and intermediates thereof*. WO 9928320.
2. Masumoto, K. et al. *SX-5216, highly potent and selective mitochondrial benzodiazepine receptor ligand as a potential anxiolytic agent*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 113.

4-IODOPROPOFOL

286269

4-Iodo-2,6-diisopropylphenol



C12 H17 I O; Mol wt: 304.1653

ACTION – A propofol analogue that is able to inhibit [35 S]-TPBS binding at the picrotoxin site on GABA_A receptors in rat brain membranes at low micromolar concentrations ($IC_{50} = 1.2$ μ M). Electrophysiological experiments with cloned $\alpha 1\beta 2\gamma 2$ GABA_A receptors indicated that compound displayed greater efficacy for potentiating GABA-elicited chloride currents ($EC_{50} = 12$ μ M) than for producing direct activation of chloride channels in the absence of GABA ($EC_{50} = 51$ μ M), a profile different from that of propofol and general anesthetics. In addition, it was shown to be more potent than propofol in inducing basal glutamate and [3 H]-norepinephrine release from rat synaptosomes. In preliminary behavioral experiments, compound, in contrast to propofol, was shown to induce anticonvulsant and anticonflict effects in rodents at doses devoid of sedation or loss of righting reflex.

SOURCES – Università degli Studi di Bari, Bari (IT); Università degli Studi di Cagliari, Cagliari (IT); Cornell University, New York, NY (US).

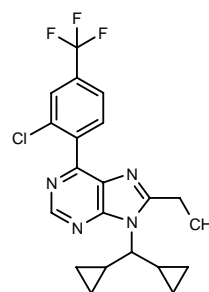
REFERENCES

1. Hemmings, H.C. et al. *Effects of propofol and 4-iodo-propofol on spontaneous release of glutamate and norepinephrine from rat cortical synaptosomes*. *Anesth Analg* 2000, 90(2, Suppl. S): Abst S-422.
2. Sanna, L. et al. *Characterization of the electrophysiological and pharmacological effects of 4-iodo-2,6-diisopropylphenol, a propofol analog devoid of sedative-anesthetic properties*. *Br J Pharmacol* 1999, 126(6): 1444.
3. Trapani, G. et al. *Propofol analogues. Synthesis, relationships between structure and affinity at GABA_A receptor in rat brain, and differential electrophysiological profile at recombinant human GABA_A receptors*. *J Med Chem* 1998, 41(11): 1846.

SV-030

287076

6-[2-Chloro-4-(trifluoromethyl)phenyl]-9-(dicyclopropylmethyl)-8-ethyl-9*H*-purine



C21 H20 Cl F3 N4; Mol wt: 420.8640

ACTION – High-affinity nonpeptide *retro*-purine corticotropin-releasing factor (CRF) receptor ($K_i = 1.8$ nM) with functional antagonist activity in an *in vitro* assay ($IC_{50} = 7.5$ nM). Compound is reported to provide high serum levels following oral administration to dogs. Potentially useful as an anxiolytic.

SOURCE – DuPont Pharmaceuticals.

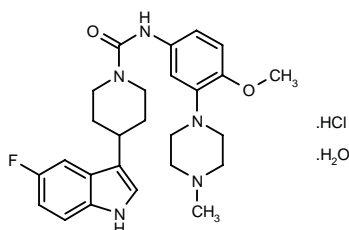
REFERENCES

1. Wilde, R.G. et al. (DuPont Pharmaceuticals Co.) *Imidazopyrimidines and imidazopyridines for the treatment of neurological disorders*. EP 0994877, WO 9901454.
2. Wilde, R.G. et al. *Retro-purines: Nonpeptide corticotropin-releasing factor receptor ligands*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 317.

TREATMENT OF MOOD DISORDERS

268437

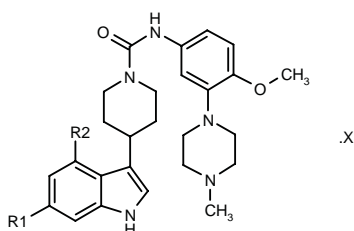
4-(5-Fluoro-1*H*-indol-3-yl)-*N*-[4-methoxy-3-(4-methyl-piperazin-1-yl)phenyl]piperidine-1-carboxamide hydrochloride hydrate



C₂₆H₃₂F N₅ O₂ · HCl · H₂O; Mol wt: 520.0455

M.p. 230-1 °C.

ACTION – Potential antidepressant, a 5-HT reuptake inhibitor (IC₅₀ = 21 nM) with 5-HT_{1B/1D} receptor-antagonist activity (pA₂ = 7.8 for blockade of the sumatriptan-induced contractile response in rat saphenous vein). Compound exhibited modest binding affinity for 5-HT_{1D}, 5-HT_{1B} and 5-HT_{1A} receptors (IC₅₀ = 233, 85 and 367 nM, respectively) and blocked sumatriptan-induced inhibition of [³H]-5-HT release in guinea pig cortical slices. Within this series of unsymmetrical ureas, the following are also included:



Compound	R1	R2	X	Formula
286831	H	F	2HCl	C ₂₆ H ₃₂ FN ₅ O ₂ ·2HCl
286832	F	H	2H ₂ O	C ₂₆ H ₃₂ FN ₅ O ₂ ·2H ₂ O

SOURCE – Merck KGaA.

REFERENCES

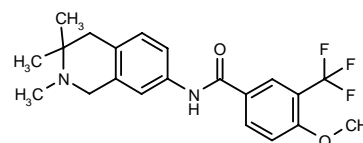
- Matzen, L. et al. (Merck Patent GmbH) *Amide and urea derivs.* DE 19756036.
- Matzen, L. et al. *5-HT reuptake inhibitors with 5-HT_{1B/1D} antagonistic activity: A new approach toward efficient antidepressants.* J Med Chem 2000, 43(6): 1149.
- Matzen, L. et al. *Potent 5-HT reuptake inhibitors with 5-HT_{1B/1D} antagonistic activity - New potential antidepressants.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.52.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

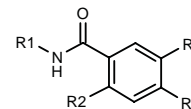
286606

4-Methoxy-3-(trifluoromethyl)-*N*-(2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)benzamide



C₂₁H₂₃F₃N₂O₂; Mol wt: 392.4187

ACTION – Anticonvulsant that binds to a novel receptor binding site labeled by [³H]-SB-204269 (pK_i > 7.5). It demonstrated potent activity in increasing seizure threshold in the maximal electroshock seizure (MES) test in rodents (340% at 2 h after a dose of 2 mg/kg p.o.). Other exemplified substituted isoquinoline derivatives include the following:



Compound	R1	R2	R3	R4	Formula
286607	2,4,4-(Me)3-1,2,3,4-tetrahydro-7-isoquinolinyl	H	OMe	Br	C ₂₀ H ₂₃ BrN ₂ O ₂
286608	2,4,4-(Me)3-1,2,3,4-tetrahydro-7-isoquinolinyl	H	OMe	I	C ₂₀ H ₂₃ IN ₂ O ₂
286609	2,4,4-(Me)3-1,2,3,4-tetrahydro-5-isoquinolinyl	OMe	i-PrO	Cl	C ₂₃ H ₂₉ ClN ₂ O ₃
286610	2,4,4-(Me)3-1,2,3,4-tetrahydro-5-isoquinolinyl	OMe	i-Pr	CF ₃	C ₂₄ H ₂₉ F ₃ N ₂ O ₂
286611	8-Et-2,4,4-(Me)3-1,2,3,4-tetrahydro-7-isoquinolinyl	H	i-PrO	Ac	C ₂₆ H ₃₄ N ₂ O ₃

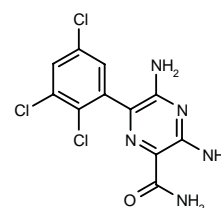
SOURCE – SmithKline Beecham.

REFERENCES

- Harling, J.D. et al. (SmithKline Beecham plc) *Subst. isoquinoline derivs. and their use as anticonvulsants.* WO 0009486.

286956

3,5-Diamino-6-(2,3,5-trichlorophenyl)pyrazine-2-carboxamide

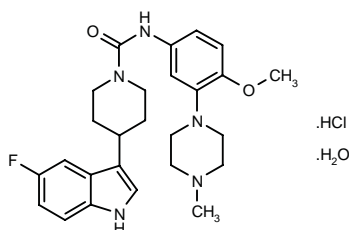


C₁₁H₈Cl₃N₅O; Mol wt: 332.5772

TREATMENT OF MOOD DISORDERS

268437

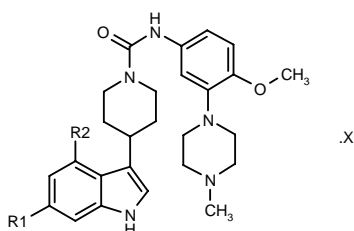
4-(5-Fluoro-1*H*-indol-3-yl)-*N*-[4-methoxy-3-(4-methyl-piperazin-1-yl)phenyl]piperidine-1-carboxamide hydrochloride hydrate



C₂₆H₃₂F N₅ O₂ · HCl · H₂O; Mol wt: 520.0455

M.p. 230-1 °C.

ACTION – Potential antidepressant, a 5-HT reuptake inhibitor (IC₅₀ = 21 nM) with 5-HT_{1B/1D} receptor-antagonist activity (pA₂ = 7.8 for blockade of the sumatriptan-induced contractile response in rat saphenous vein). Compound exhibited modest binding affinity for 5-HT_{1D}, 5-HT_{1B} and 5-HT_{1A} receptors (IC₅₀ = 233, 85 and 367 nM, respectively) and blocked sumatriptan-induced inhibition of [³H]-5-HT release in guinea pig cortical slices. Within this series of unsymmetrical ureas, the following are also included:



Compound	R1	R2	X	Formula
286831	H	F	2HCl	C ₂₆ H ₃₂ FN ₅ O ₂ ·2HCl
286832	F	H	2H ₂ O	C ₂₆ H ₃₂ FN ₅ O ₂ ·2H ₂ O

SOURCE – Merck KGaA.

REFERENCES

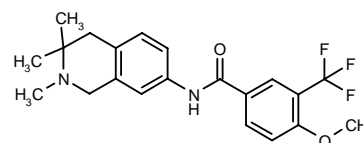
- Matzen, L. et al. (Merck Patent GmbH) *Amide and urea derivs.* DE 19756036.
- Matzen, L. et al. *5-HT reuptake inhibitors with 5-HT_{1B/1D} antagonistic activity: A new approach toward efficient antidepressants.* J Med Chem 2000, 43(6): 1149.
- Matzen, L. et al. *Potent 5-HT reuptake inhibitors with 5-HT_{1B/1D} antagonistic activity - New potential antidepressants.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.52.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

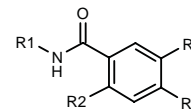
286606

4-Methoxy-3-(trifluoromethyl)-*N*-(2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)benzamide



C₂₁H₂₃F₃N₂O₂; Mol wt: 392.4187

ACTION – Anticonvulsant that binds to a novel receptor binding site labeled by [³H]-SB-204269 (pK_i > 7.5). It demonstrated potent activity in increasing seizure threshold in the maximal electroshock seizure (MES) test in rodents (340% at 2 h after a dose of 2 mg/kg p.o.). Other exemplified substituted isoquinoline derivatives include the following:



Compound	R1	R2	R3	R4	Formula
286607	2,4,4-(Me) ₃ -1,2,3,4-tetrahydro-7-isoquinolinyl	H	OMe	Br	C ₂₀ H ₂₃ BrN ₂ O ₂
286608	2,4,4-(Me) ₃ -1,2,3,4-tetrahydro-7-isoquinolinyl	H	OMe	I	C ₂₀ H ₂₃ IN ₂ O ₂
286609	2,4,4-(Me) ₃ -1,2,3,4-tetrahydro-5-isoquinolinyl	OMe	i-PrO	Cl	C ₂₃ H ₂₉ ClN ₂ O ₃
286610	2,4,4-(Me) ₃ -1,2,3,4-tetrahydro-5-isoquinolinyl	OMe	i-Pr	CF ₃	C ₂₄ H ₂₉ F ₃ N ₂ O ₂
286611	8-Et-2,4,4-(Me) ₃ -1,2,3,4-tetrahydro-7-isoquinolinyl	H	i-PrO	Ac	C ₂₆ H ₃₄ N ₂ O ₃

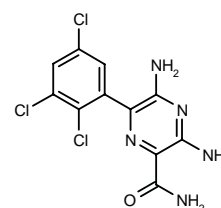
SOURCE – SmithKline Beecham.

REFERENCES

- Harling, J.D. et al. (SmithKline Beecham plc) *Subst. isoquinoline derivs. and their use as anticonvulsivants.* WO 0009486.

286956

3,5-Diamino-6-(2,3,5-trichlorophenyl)pyrazine-2-carboxamide



C₁₁H₈Cl₃N₅O; Mol wt: 332.5772

ACTION – Anticonvulsant, a sodium channel blocker reported to possess increased anticonvulsant potency compared to lamotrigine and increased selectivity in terms of CNS side effects and inhibition of dihydrofolate reductase. A specifically claimed compound from a series of pyrazine derivatives.

SOURCE – Glaxo Wellcome.

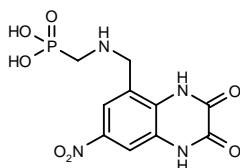
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AMP-397A

286885

(7-Nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethylaminomethyl)phosphonic acid



C10 H13 N4 O7 P; Mol wt: 332.2077

ACTION – Antiepileptic agent, a competitive AMPA receptor antagonist with high affinity for the receptor ($IC_{50} = 11$ nM against [3H]-CNQX binding) and selectivity over kainate receptors ($IC_{50} = 4200$ nM). Compound demonstrated anticonvulsant activity in a wide range of animal models of epilepsy including electroshock and chemically induced seizures in mice and genetically epilepsy-prone rats. In addition, it was shown to delay the development of kindling and to reduce seizure severity in fully kindled rats.

SOURCE – Novartis.

REFERENCES

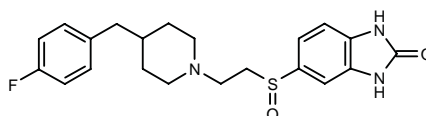
1. Acklin, P. et al. (Novartis AG) *Substd. aminoalkane phosphonic acids.* EP 0934326, WO 9817672.
2. Auberson, Y.P. *AMP397A: Novel, broad-spectrum anticonvulsant with potential benefit for therapy-resistant epileptic patients.* 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 14.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

PD-196860

287036

5-[2-[4-(4-Fluorobenzyl)piperidin-1-yl]ethylsulfanyl]-2,3-dihydro-1H-benzimidazol-2-one



C21 H24 F N3 O2 S; Mol wt: 401.5036

ACTION – Potent subtype-selective NR1/2B NMDA receptor antagonist ($IC_{50} = 30$ nM) reported to be active in a preclinical model of Parkinson's disease.

SOURCES – CoCensys; Warner-Lambert (Pfizer).

REFERENCES

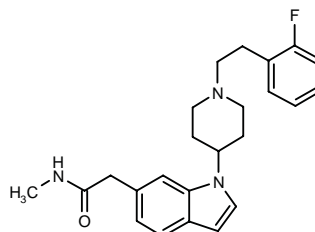
1. Wright, J.L. et al. (Warner-Lambert Co.; CoCensys Inc.) *4-Benzyl piperidine alkylsulfoxide heterocycles and their use as subtype-selective NMDA receptor antagonists.* WO 0000197.
2. Kesten, S.R. et al. *Syntheses and SAR of 4-benzyl piperidinyl alkyl heteroatom linked heterocycles as subtype selective NMDA receptor antagonists.* 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 94.

ANTISPASTIC DRUGS AND DRUGS FOR MUSCLE SPASMS

E-2101^{1,5-8}

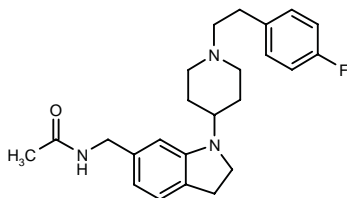
279125

2-[1-[1-[2-(2-Fluorophenyl)ethyl]piperidin-4-yl]-1H-indol-6-yl]-N-methylacetamide



C24 H28 F N3 O; Mol wt: 393.5032

ACTION – Centrally acting muscle relaxant, a dual antagonist at 5-HT_{1A} and 5-HT₂ receptors with nanomolar affinity (K_i = 4 and 1.2 nM, respectively), as well as good selectivity over α_1 -adrenoceptors and dopamine D₂ receptors (K_i = 85 and 152 nM, respectively). It exhibited 5-HT₂-antagonist activity *in vivo*, as demonstrated by inhibition of tryptamine-induced head twitches in mice. Compound showed muscle relaxant activity in two *in vivo* models of spasticity: the intercollicular-lesioned decerebrated rat model (ID_{50} = 0.05 mg/kg i.v.) and morphine-induced Straub tail response in mice (ED_{50} = 1 mg/kg p.o.). It did not influence barbitol-induced sleep and only at high doses was an excessive reduction in muscle tone seen. Potentially useful for the treatment of muscular rigidity caused by different pathological states including stroke, spinal cord injury and multiple sclerosis. Another related compound is:



E-2100 [269673]*,1-4,7: C₂₄ H₃₀ F N₃ O

SOURCE – Eisai.

REFERENCES

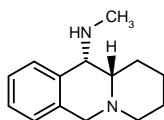
1. Kitazawa, N. et al. (Eisai Co., Ltd.) *1,4-Substd. cyclic amine derivs.* EP 0976732, WO 9843956.
2. Miyazawa, M. and Chiba, H. (Eisai Co., Ltd.) *Preparation method of amine derivs.* JP 1999246552.
3. Ueno, K. et al. (Eisai Co., Ltd.) *Analgesics.* WO 0023075.
4. Urawa, Y. et al. (Eisai Co., Ltd.) *Preparation method of nitril derivs.* JP 1999209373.
5. Kubota, A. et al. *Pharmacological profile of E2101, a new centrally acting muscle relaxant.* FASEB J 2000, 14(8): Abst 516.
6. Matsunaga, M. et al. *Analgesic property of E2101 and a role of 5HT receptors in nociceptive transmission.* FASEB J 2000, 14(8): Abst 38.
7. Ueno, K. et al. *Synthesis and evaluation of indoline and indole derivatives as a dual antagonist for 5-HT_{1A} and 5-HT₂ receptor.* 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 97.
8. *Three new clinical candidates enter the pipeline at Eisai.* DailyDrugNews.com (Daily Essentials) 1999, Oct 12.

*Identified compound **269673** (see **269670**) Drug Data Rep 1998, 020(11): 0928.

COGNITION-ENHANCING DRUGS

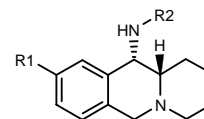
286212

trans-N-Methyl-2,3,4,6,11,11a-hexahydro-1H-benzo[b]-quinolizin-11-amine



C₁₄ H₂₀ N₂; Mol wt: 216.3260

ACTION – Agent for the treatment of Alzheimer's disease, senile dementia and other conditions characterized by memory loss, proven to protect against scopolamine-induced amnesia in rats. Compound was found to be a weak inhibitor of acetylcholinesterase and is reported to show less potential for producing hepatotoxicity than tacrine. Other compounds from this series of benzoquinolizidine and benzoindolizidine derivatives include the following:



Compound	R1	R2	Formula
286213	OMe	Me	C ₁₅ H ₂₂ N ₂ O
286214	H	CH ₂ Ph	C ₂₀ H ₂₄ N ₂
286215	H	H	C ₁₃ H ₁₈ N ₂

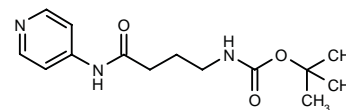
SOURCE – American Biogenetic Sciences.

REFERENCES

1. Szmuszkovicz, J. and Regan, C.M. (American Biogenetic Sciences, Inc.) *Benzoquinolizidine and benzoindolizidine derivs. and therapeutic uses thereof.* WO 0004905.

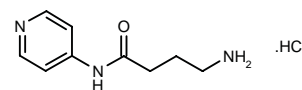
286274

N-[4-Oxo-4-(4-pyridinylamino)butyl]carbamic acid *tert*-butyl ester



C₁₄ H₂₁ N₃ O₃; Mol wt: 279.3379

ACTION – Cognition-enhancing agent, a 4-aminopyridine derivative with potent anti-amnesic activity at doses of 0.4-4 μ mol/kg p.o. in CO₂-induced amnesia in mice when compared to the reference drug piracetam. Another related compound is:



286275: C₉ H₁₃ N₃ O . HCl

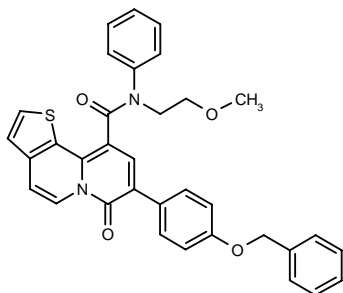
SOURCE – Chiesi.

REFERENCES

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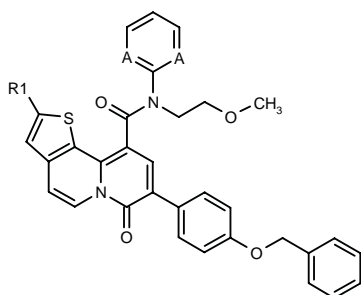
286557

8-[4-(Benzyloxy)phenyl]-*N*-(2-methoxyethyl)-7-oxo-*N*-phenyl-7*H*-thieno[2,3-*a*]quinolizine-10-carboxamide



C₃₄ H₂₈ N₂ O₄ S; Mol wt: 560.6712

ACTION – Agent for the treatment or prevention of Alzheimer's disease that inhibits β -amyloid ($A\beta$) peptide formation, as demonstrated indirectly via inhibition of the activity of mutated β -amyloid precursor protein (β -APP) in HEK cells (IC_{50} = 0.5 μ M). Other specifically claimed compounds from this series of bi- and tricyclic pyridone derivatives include the following:



Compound	R1	A	Formula
286558	Me	CH	C ₃₅ H ₃₀ N ₂ O ₄ S
286559	H	N	C ₃₂ H ₂₆ N ₄ O ₄ S

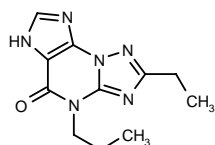
SOURCE – Roche.

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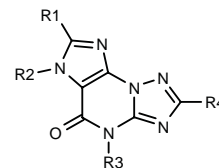
286997

2-Ethyl-4-propyl-5,6-dihydro-4*H*-[1,2,4]triazolo[5,1-*b*]-purin-5-one

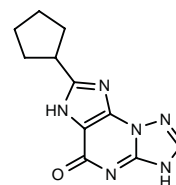


C₁₁ H₁₄ N₆ O; Mol wt: 246.2726

ACTION – Adenosine A₁ receptor antagonist (K_i = 2.1 nM) with potential in the treatment of CNS disorders such as Alzheimer's disease and depression, as well as asthma and cardiovascular and renal disorders. Other compounds from this series of imidazotriazolopyrimidines include the following:



Compound	R1	R2	R3	R4	Formula
286998	CH ₂ Ph	H	Pr	H	C ₁₆ H ₁₆ N ₆ O
286999	cyclopentyl	H	Bu	H	C ₁₅ H ₂₀ N ₆ O
287001	H	Pr	Pr	cyclopentyl	C ₁₇ H ₂₄ N ₆ O
287002	cyclopentyl	H	Pr	cyclopentyl	C ₁₉ H ₂₆ N ₆ O
287006	cyclopentyl	Me	Me	H	C ₁₃ H ₁₆ N ₆ O
287007	cyclopentyl	H	Pr	H	C ₁₄ H ₁₈ N ₆ O
287009	3-THF	H	Pr	cyclopentyl	C ₁₈ H ₂₄ N ₆ O ₂
287011	CH ₂ Ph	H	Pr	cyclopentyl	C ₂₁ H ₂₄ N ₆ O



287005: C₁₁ H₁₂ N₆ O

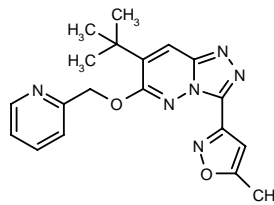
SOURCE – Boehringer Ingelheim.

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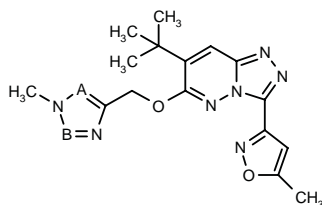
287077

7-*tert*-Butyl-3-(5-methylisoxazol-3-yl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine



C₁₉ H₂₀ N₆ O₂; Mol wt: 364.4070

ACTION – Selective GABA_A receptor ligand that is reported to act as an inverse agonist at the $\alpha 5$ subtype (K_i = 100 nM or less), with potential in the treatment of cognitive disorders such as Alzheimer's disease. Other compounds within the scope of the patent are reported to exhibit high affinity for the $\alpha 2$ and/or $\alpha 3$ subunits and are therefore suitable for the treatment or prevention of CNS disorders, particularly anxiety and convulsions. Other exemplified compounds within this series of triazolo-pyridazine derivatives include the following:



Compound	A	B	Formula
287079	N	CH	C ₁₇ H ₂₀ N ₆ O ₂
287080	CH	N	C ₁₇ H ₂₀ N ₆ O ₂

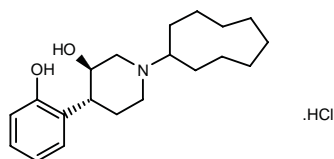
SOURCE – Merck Sharp & Dohme.

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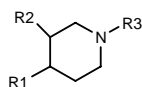
287302

trans-1-Cyclononyl-4-(2-hydroxyphenyl)piperidin-3-ol hydrochloride



C20 H31 N O2 . HCl; Mol wt: 353.9308

ACTION – N/OFQ (ORL1) receptor modulator ($pK_i = 7.5$ in HEK293 cells transfected with rat N/OFQ receptors) with potential in the treatment of memory and attention deficits, anxiety, stress disorders, depression, memory loss due to Alzheimer's disease or other dementias, Parkinson's disease, epilepsy and convulsions, acute and/or chronic pain, drug withdrawal symptoms, control of water balance and Na⁺ excretion, arterial blood pressure disorders and metabolic disorders such as obesity. Other specifically claimed compounds from this series of piperidine derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
287303	2-MeO-Ph	H	cyclodecyl		C ₂₂ H ₃₅ NO
287304	2-i-Pr-Ph	OH	cyclodecyl	trans	C ₂₄ H ₃₉ NO ₂
287305	2-OH-Ph	OH	4-i-Pr-cyclohexyl	trans	C ₂₀ H ₃₁ NO ₂
287306	2-OH-Ph	H	cyclodecyl		C ₂₁ H ₃₃ NO
287307	2-MeO-Ph	OH	cyclodecyl	trans	C ₂₂ H ₃₅ NO ₂
287308	cyclohexyl	H	cyclodecyl		C ₂₁ H ₃₉ N
287309	2-MeO-Ph	OH	cyclononyl	trans	C ₂₁ H ₃₃ NO ₂
287310	2-(allyl-O)-Ph	OH	cyclodecyl	trans	C ₂₄ H ₃₇ NO ₂
287311	Ph	H	cyclodecyl		C ₂₁ H ₃₃ N
287312	2-i-Pr-Ph	OH	cyclononyl	trans	C ₂₃ H ₃₇ NO ₂
287313	2-OH-Ph	OH	cyclodecyl	trans	C ₂₁ H ₃₃ NO ₂

SOURCE – Roche.

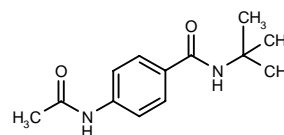
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CPI-1189*

283852

4-Acetamido-*N*-(*tert*-butyl)benzamide



C13 H18 N2 O2; Mol wt: 234.2972

ACTION – Neuroprotective agent, an analogue of the nitron-based spin trapping agent PBN that inhibits p38 mitogen-activated protein (MAP) kinase phosphorylation (70-80% inhibition at 10-300 nM in primary rat astrocyte cultures stimulated with IL-1 β) and TNF- α -mediated neuronal apoptosis in animal models of HIV-induced dementia; compound was also shown to protect against dextran sulfate sodium-induced colitis in mice. Currently undergoing phase II clinical trials in patients with AIDS dementia complex and Parkinson's disease.

SOURCE – Centaur.

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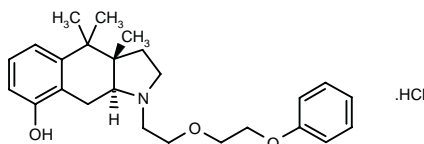
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4. Flitter, W.D. et al. *Intraventricular TNF- α infusion as a model of AIDS dementia. II. Induction of apoptosis prevented by CPI-1189*. Soc Neurosci Abst 1997, 23(1-2): Abst 326.5.
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9. *Centaur's treatment for AIDS dementia making steady progress in phase II*. DailyDrugNews.com (Daily Essentials) 2000, April 28.

*Identified compound **283852** Drug Data Rep 2000, 022(03): 0248.

TREATMENT OF CEREBROVASCULAR DISEASES

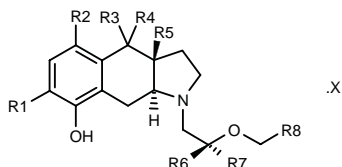
286376

(-)-*trans*-3a,4,4-Trimethyl-1-[2-(2-phenoxyethoxy)ethyl]-2,3,3a,4,9,9a-hexahydro-1*H*-benzo[*f*]indol-8-ol hydrochloride



C₂₅ H₃₃ N O₃ · HCl; Mol wt: 432.0006

ACTION – Voltage-dependent sodium channel blocker with potential in the treatment of arrhythmia, cardiac and cerebral ischemia, neurodegenerative disorders, hypoglycemia, hypoxia, anoxia, brain trauma, cerebral edema, stroke, amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, myocardial infarction and angina pectoris. Other compounds from this series of 2,3,3a,4,9,9a-hexahydro-8-hydroxy-1*H*-benz[*f*]indoles include the following:



Compound	R1	R2	R3=R4=R5	R6	R7	R8	X	Isomer	Formula
286377	H	H	Me	H	Me	Ph	HCl	(-)	C ₂₅ H ₃₃ NO ₂ ·HCl
286378	H	H	H	H	H	CH ₂ OPh	oxalate	(±)	C ₂₂ H ₂₇ NO ₃ ·C ₂ H ₂ O ₄
286379	Cl	H	Me	Me	H	Ph	HCl	(-)	C ₂₅ H ₃₂ ClNO ₂ ·HCl
286380	H	Cl	Me	Me	H	Ph	HCl	(-)	C ₂₅ H ₃₂ ClNO ₂ ·HCl

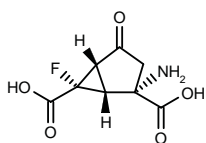
SOURCE – Boehringer Ingelheim.

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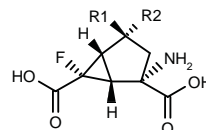
286777

(+)-(1*R**,2*S**,5*S**,6*S**)-2-Amino-6-fluoro-4-oxobicyclo-[3.1.0]hexane-2,6-dicarboxylic acid



C₈ H₈ F N O₅; Mol wt: 217.1512

ACTION – Group 2 metabotropic glutamate receptor (mglu₂) agonist, as demonstrated in a functional assay measuring its effect on forskolin-stimulated cAMP accumulation in mglu₂-expressing CHO cells (ED₅₀ = 0.66 nM). Potentially useful in the treatment or prevention of schizophrenia, anxiety, depression, bipolar disorder, drug addiction, cognitive disorders, Alzheimer's disease, Huntington's disease, Parkinson's disease, movement disorders associated with muscle rigidity, brain ischemia, and spinal cord and head trauma. Other compounds from this series of 6-fluorobicyclo[3.1.0]hexane derivatives include the following:



Compound	R1	R2	Isomer	Formula
286778	H	H	racemic	C ₈ H ₁₀ FNO ₄
286779	H	H	(-)	C ₈ H ₁₀ FNO ₄
286780	-O-		racemic	C ₈ H ₈ FNO ₅
286781	OH	H	racemic	C ₈ H ₁₀ FNO ₅

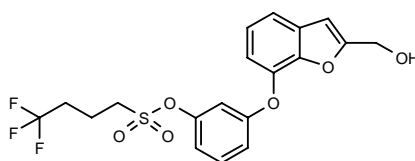
SOURCE – Taisho.

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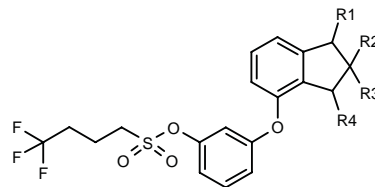
286821

4,4,4-Trifluorobutane-1-sulfonic acid 3-[2-(hydroxymethyl)-1-benzofuran-7-yloxy]phenyl ester



C₁₉ H₁₇ F₃ O₆ S; Mol wt: 430.3973

ACTION – Agent for the treatment and prevention of neurodegenerative diseases, especially stroke, brain trauma, pain, migraine and spasticity, with cannabinoid CB₁ receptor-agonist activity (IC₅₀ = 0.55 nM in a rat CB₁ receptor-luciferase reporter gene assay). Other specifically claimed compounds from this series of aryl sulfonamides include the following:



Compound	R1	R2	R3	R4	Formula
286822	bond		CO ₂ Me	H	C ₂₁ H ₁₉ F ₃ O ₆ S
286823	H	CO ₂ Me	bond		C ₂₁ H ₁₉ F ₃ O ₆ S
286824	bond		CH ₂ OH	H	C ₂₀ H ₁₉ F ₃ O ₆ S
286825	H	CH ₂ OH	bond		C ₂₀ H ₁₉ F ₃ O ₆ S

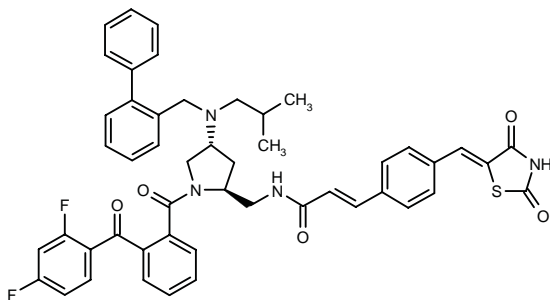
SOURCE – Bayer.

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286828

N-[4(*R*)-[*N*-(Biphenyl-2-ylmethyl)-*N*-isobutylamino]-1-[2(*S*)-(2,4-difluorobenzoyl)benzoyl]pyrrolidin-2-ylmethyl]-3-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenyl]-2(*E*)-propenamide



C49 H44 F2 N4 O5 S; Mol wt: 838.9716

ACTION – Nonpeptide cytosolic phospholipase $A_{2\alpha}$ (cPLA $_{2\alpha}$) inhibitor (IC_{50} = 1.8 nM against human enzyme) proven to inhibit the release of arachidonic acid, PGE $_2$ and LTC $_4$ in A23187-stimulated THP-1 cells (IC_{50} = 22, 31 and 13 nM, respectively). Potentially useful for the treatment of inflammatory diseases and stroke.

SOURCE – Shionogi.

REFERENCES

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287095

L-Leucyl-L-leucyl-L-aspartyl-L-asparaginyl-L-asparaginyl-L-lysyl-L-threonyl-L-glutamyl-L-lysyl-L-leucyl-L-tyrosine *N*-2.1-C-1.11-lactam

C60 H97 N15 O19; Mol wt: 1332.5120

ACTION – Cyclic prosaposin-derived peptide reported to exhibit good resistance to proteolytic degradation and to be capable of crossing the blood-brain barrier, with potential in the promotion of neurite outgrowth, prevention of cell death, promotion of myelination, as well as for the treatment or prevention of neurodegenerative disorders and neuropathic pain. *In vitro*, compound induced neurite outgrowth in neuroblastoma NS20Y cells (EC_{50} = 0.6 ng/ml) and prevented death of these cells (EC_{50} = 0.6 ng/ml), being more potent than TX14(A) (EC_{50} = 1.0 and 1.0 ng/ml, respectively). Another specifically claimed peptide is:

L-Leucyl-L-isoleucyl-L-asparaginyl-L-alanyl-L-threonyl-L-glutamyl-L-glutamyl-L-isoleucyl-L-leucine *N*-2.1-C-1.11-lactam

287096: C53 H87 N13 O20

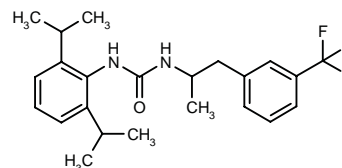
SOURCE – Myelos Neurosciences.

REFERENCES

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287514

N-(2,6-Diisopropylphenyl)-*N'*-[1-methyl-2-[3-(trifluoromethyl)phenyl]ethyl]urea



C23 H29 F3 N2 O; Mol wt: 406.4891

ACTION – Potent and selective N-type calcium channel blocker (IC_{50} = 1.6 μ M in human neuroblastoma IMR-32 cells) shown to block (74% at 1 μ M) currents at recombinant B-class N-type Ca $^{2+}$ channels in S-3 cells. In the audiogenic seizure model in DBA/2 mice, compound (60 mg/kg p.o.) provided 20% and 40% neuroprotection, respectively, at 30 and 60 min after treatment. Potentially useful for the treatment or prevention of cerebral ischemia and pain.

SOURCES – Elan; Warner-Lambert (Pfizer).

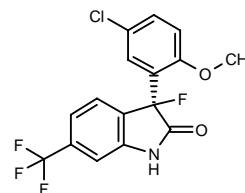
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BMS-204352

273916

(+)-3(*S*)-(5-Chloro-2-methoxyphenyl)-3-fluoro-6-(trifluoromethyl)-2,3-dihydro-1*H*-indol-2-one



C16 H10 Cl F4 N O2; Mol wt: 359.7050

ACTION – Neuroprotective agent, a transmembrane potassium channel modulator that acts as an opener of large-conductance, calcium-activated potassium (maxi-K) channels (EC_{50} = 352 nM). Compound was shown to protect neurons through regulation of potentially pathogenic neurotransmitter release, and is currently in phase III clinical trials in patients with acute ischemic stroke.

SOURCE – Bristol-Myers Squibb.

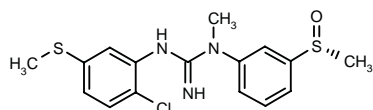
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CNS-5788

286966

(+)-*N*¹-[2-Chloro-5-(methylsulfonyl)phenyl]-*N*³-methyl-*N*³-[3-[(*R*)-methylsulfinyl]phenyl]guanidine



C₁₆ H₁₈ Cl N₃ O₂; Mol wt: 367.9232

ACTION – Ischemia-selective NMDA receptor antagonist, the active enantiomer of CNS-5655 and an ischemia-activated prodrug of CNS-5161⁺. Compound exhibited strong neuroprotection in animal models of ischemia such as rat pup hypoxia (100% neuroprotection at 20 mg/kg i.p.) and a rat middle cerebral artery occlusion stroke model (22% protection at 9 mg/kg i.p.).

SOURCE – Cambridge NeuroScience.

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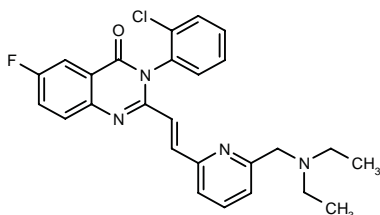
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*Drug Data Rep 1998, 020(02): 0122.

CP-465022*

259496

(+)-(a*S*)-(2-Chlorophenyl)-2-[(*E*)-2-[6-(diethylamino-methyl)pyridin-2-yl]vinyl]-6-fluoroquinazolin-4(3*H*)-one



C₂₆ H₂₄ Cl F N₄ O; Mol wt: 462.9536

ACTION – Neuroprotective agent, a potent, non-competitive AMPA receptor antagonist proven to inhibit AMPA-mediated ⁴⁵Ca²⁺ uptake in primary cultures of rat cerebellar granules, hippocampal and cortical neurons (IC₅₀ = 20-40 nM) and to inhibit kainate-activated currents in whole-cell patch recordings from rat cortical neurons (IC₅₀ = 30 nM). In anesthetized rats, compound (i.v. and s.c.) dose-dependently reduced the population spike amplitude evoked by constant-voltage stimulation of the commissural pathway. It also dose-dependently antagonized tonic seizures produced by pentylentetrazol in mice (ID₅₀ = 3.1 mg/kg s.c.) and rats (ID₅₀ = 1.0 mg/kg s.c.), and it antagonized AMPA-induced clonic seizures in mice with similar efficacy (1.5 mg/kg s.c.).

SOURCE – Pfizer.

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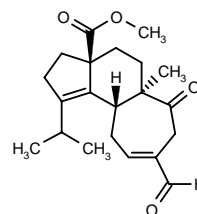
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*Identified compound **259496** (see **258990**) Drug Data Rep 1998, 020(03): 0211.

SCABRONINE G METHYL ESTER^{2,4}

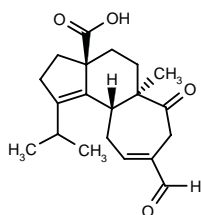
286882

(3a*S*,5a*R*,10a*R*)-8-Formyl-1-isopropyl-5a-methyl-6-oxo-3,4,5,6,7,10,10a-octahydro-2*H*-cyclohept[e]indene-3a-carboxylic acid methyl ester



C₂₁ H₂₈ O₄; Mol wt: 344.4482

ACTION – Synthetic derivative of **scabronine G**, a neurotrophic factor that significantly promotes the synthesis and secretion of nerve growth factor (NGF) and IL-6 from human astrocytoma 1321NI cells, an effect associated with activation of protein kinase C ζ (PKC ζ).



Scabronine G [286871]¹⁻⁴: C₂₀ H₂₆ O₄

SOURCES – Kanazawa University, Kanazawa (JP); Tohoku University, Sendai (JP).

REFERENCES

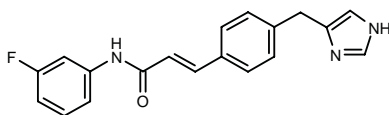
1. Oshima, Y. et al. (Kagome Co., Ltd.) *Cyathane derivs. and nerve growth factor (NGF) production inducers containing them as active ingredient*. JP 1999269125.
2. Obara, Y. et al. *Scabronine promotes the secretion of neurotrophic factor from 1321N1 human astrocytoma cells accompanied by the activation of PKC*. Jpn J Pharmacol 2000, 82(Suppl. 1): Abst P-502.
3. Obara, Y. et al. *Stimulation of neurotrophic factor secretion from 1321N1 human astrocytoma cells by novel diterpenoids, scabronines A and G*. Eur J Pharmacol 1999, 370(1): 79.
4. Ohta, T. et al. *Stereostructures for diterpenoids having inductive activity of the nerve growth factor synthesis, from Sarcodon scabrosus*. Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 1998, 40: 341.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

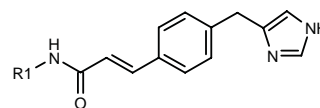
286664

N-(3-Fluorophenyl)-3-[4-(1*H*-imidazol-4-ylmethyl)phenyl]-2(*E*)-propenamide



C₁₉ H₁₆ F N₃ O; Mol wt: 321.3534

ACTION – Histamine H₃ receptor antagonist (K_i = 1 nM in a binding assay using guinea pig brain receptors) for the treatment of allergy-induced upper airways responses, particularly in combination with a histamine H₁ receptor antagonist such as loratadine or descarboethoxy-loratadine, as well as inflammation, cardiovascular disease, hypotension, glaucoma, sleep disorders, gastrointestinal disorders, CNS disorders, Alzheimer's disease, schizophrenia, obesity and migraine. Other exemplified phenyl-alkyl-imidazoles are:



Compound	R1	Formula
286665	4-Cl-Ph	C ₁₉ H ₁₆ ClN ₃ O
286666	4-Cl-PhCH ₂ CH ₂	C ₂₁ H ₂₀ ClN ₃ O
286667	Ph	C ₁₉ H ₁₇ N ₃ O
286668	4-MeO-PhCH ₂ CH ₂	C ₂₂ H ₂₃ N ₃ O ₂
286669	4-Me-PhCH ₂ CH ₂	C ₂₂ H ₂₃ N ₃ O
286670	3-Cl-Ph	C ₁₉ H ₁₆ ClN ₃ O
286671	3-CN-Ph	C ₂₀ H ₁₆ N ₄ O
286672	3-MeO-Ph	C ₂₀ H ₁₉ N ₃ O ₂
286673	3,5-(Me)2-Ph	C ₂₁ H ₂₁ N ₃ O
286674	4-F-Ph	C ₁₉ H ₁₆ FN ₃ O
286675	3-CF ₃ O-Ph	C ₂₀ H ₁₆ F ₃ N ₃ O ₂

SOURCE – Schering-Plough.

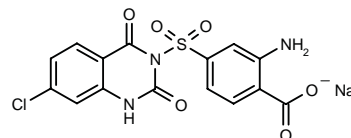
REFERENCES

1. Aslanian, R.G. et al. (Schering Corp.) *Phenyl-alkyl-imidazoles*. US 6034251.

ASTHMA THERAPY

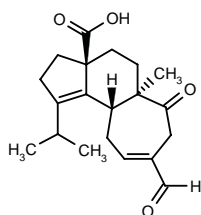
286917

2-Amino-4-(7-chloro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-ylsulfonyl)benzoic acid sodium salt



C₁₅ H₉ Cl N₃ Na O₆ S; Mol wt: 417.7601

ACTION – Agent for the treatment or prevention of allergic or rheumatic diseases such as bronchial asthma, eczema, atopic dermatitis or rheumatoid arthritis, as well as cardiac and circulatory system disorders due to excess angiotensin II production such as heart failure, hypertension, restenosis following percutaneous transluminal coronary angioplasty (PTCA), myocardial infarction, arteriosclerosis and diabetic or nondiabetic renal diseases, a chymase inhibitor with the ability to suppress chymase-induced exacerbation of vascular permeability. *In vitro*, compound was shown to inhibit human heart chymase with an IC₅₀ of 0.14 μM. In addition, it was shown to inhibit the human chymase-induced increase in vascular permeability by 64% in rats at 10 mg/kg p.o. Its half-life in human plasma was found to be 103 min. A representative compound from a series of quinazoline derivatives, wherein the following are also included:



Scabronine G [286871]¹⁻⁴: C₂₀ H₂₆ O₄

SOURCES – Kanazawa University, Kanazawa (JP); Tohoku University, Sendai (JP).

REFERENCES

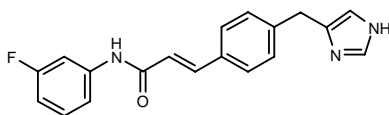
1. Oshima, Y. et al. (Kagome Co., Ltd.) *Cyathane derivs. and nerve growth factor (NGF) production inducers containing them as active ingredient*. JP 1999269125.
2. Obara, Y. et al. *Scabronine promotes the secretion of neurotrophic factor from 1321N1 human astrocytoma cells accompanied by the activation of PKC*. Jpn J Pharmacol 2000, 82(Suppl. 1): Abst P-502.
3. Obara, Y. et al. *Stimulation of neurotrophic factor secretion from 1321N1 human astrocytoma cells by novel diterpenoids, scabronines A and G*. Eur J Pharmacol 1999, 370(1): 79.
4. Ohta, T. et al. *Stereostructures for diterpenoids having inductive activity of the nerve growth factor synthesis, from Sarcodon scabrosus*. Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 1998, 40: 341.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

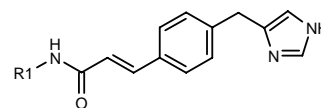
286664

N-(3-Fluorophenyl)-3-[4-(1*H*-imidazol-4-ylmethyl)phenyl]-2(*E*)-propenamide



C₁₉ H₁₆ F N₃ O; Mol wt: 321.3534

ACTION – Histamine H₃ receptor antagonist (K_i = 1 nM in a binding assay using guinea pig brain receptors) for the treatment of allergy-induced upper airways responses, particularly in combination with a histamine H₁ receptor antagonist such as loratadine or descarboethoxy-loratadine, as well as inflammation, cardiovascular disease, hypotension, glaucoma, sleep disorders, gastrointestinal disorders, CNS disorders, Alzheimer's disease, schizophrenia, obesity and migraine. Other exemplified phenyl-alkyl-imidazoles are:



Compound	R1	Formula
286665	4-Cl-Ph	C ₁₉ H ₁₆ ClN ₃ O
286666	4-Cl-PhCH ₂ CH ₂	C ₂₁ H ₂₀ ClN ₃ O
286667	Ph	C ₁₉ H ₁₇ N ₃ O
286668	4-MeO-PhCH ₂ CH ₂	C ₂₂ H ₂₃ N ₃ O ₂
286669	4-Me-PhCH ₂ CH ₂	C ₂₂ H ₂₃ N ₃ O
286670	3-Cl-Ph	C ₁₉ H ₁₆ ClN ₃ O
286671	3-CN-Ph	C ₂₀ H ₁₆ N ₄ O
286672	3-MeO-Ph	C ₂₀ H ₁₉ N ₃ O ₂
286673	3,5-(Me)2-Ph	C ₂₁ H ₂₁ N ₃ O
286674	4-F-Ph	C ₁₉ H ₁₆ FN ₃ O
286675	3-CF ₃ O-Ph	C ₂₀ H ₁₆ F ₃ N ₃ O ₂

SOURCE – Schering-Plough.

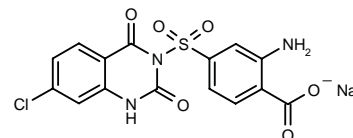
REFERENCES

1. Aslanian, R.G. et al. (Schering Corp.) *Phenyl-alkyl-imidazoles*. US 6034251.

ASTHMA THERAPY

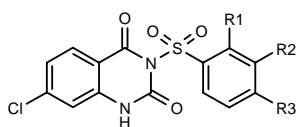
286917

2-Amino-4-(7-chloro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-ylsulfonyl)benzoic acid sodium salt



C₁₅ H₉ Cl N₃ Na O₆ S ; Mol wt: 417.7601

ACTION – Agent for the treatment or prevention of allergic or rheumatic diseases such as bronchial asthma, eczema, atopic dermatitis or rheumatoid arthritis, as well as cardiac and circulatory system disorders due to excess angiotensin II production such as heart failure, hypertension, restenosis following percutaneous transluminal coronary angioplasty (PTCA), myocardial infarction, arteriosclerosis and diabetic or nondiabetic renal diseases, a chymase inhibitor with the ability to suppress chymase-induced exacerbation of vascular permeability. *In vitro*, compound was shown to inhibit human heart chymase with an IC₅₀ of 0.14 μM. In addition, it was shown to inhibit the human chymase-induced increase in vascular permeability by 64% in rats at 10 mg/kg p.o. Its half-life in human plasma was found to be 103 min. A representative compound from a series of quinazoline derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
286918	NH ₂	H	H	C ₁₄ H ₁₀ ClN ₃ O ₄ S
286919	H	NH ₂	CO ₂ H	C ₁₅ H ₁₀ ClN ₃ O ₆ S

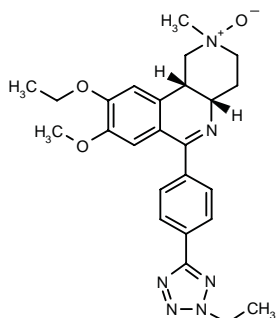
SOURCE – Suntory.

REFERENCES

1. Fukami, H. et al. (Suntory Ltd.) *Quinazoline derivs. and pharmaceutical application thereof*. WO 0010982.

286963

cis-9-Ethoxy-6-[4-(2-ethyl-2*H*-tetrazol-5-yl)phenyl]-8-methoxy-2-methyl-1,2,3,4,4a,10b-hexahydrobenzo-[c][1,6]naphthyridine *N*²-oxide



C₂₅ H₃₀ N₆ O₃; Mol wt: 462.5510

ACTION – Phosphodiesterase type 3 (PDE3) and 4 (PDE4) inhibitor (–log IC₅₀ = 6.11 and 7.53, respectively), with potential in the treatment of inflammatory airways disorders and dermatosis. A representative compound from a series of benzonaphthyridine *N*-oxide derivatives.

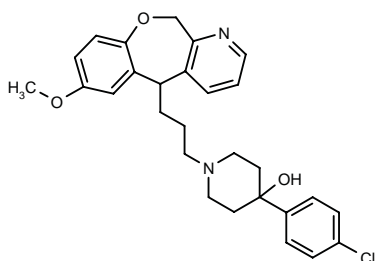
SOURCE – Byk Gulden.

REFERENCES

1. Gutterer, B. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Benzonaphthyridine-N-oxides comprising a PDE3 and PDE4 inhibiting activity*. WO 0012501.

287211

4-(4-Chlorophenyl)-1-[3-(7-methoxy-5,11-dihydro[1]-benzoxepino[3,4-*b*]pyridin-5-yl)propyl]piperidin-4-ol



C₂₈ H₃₁ Cl N₂ O₃; Mol wt: 479.0169

ACTION – Chemokine CCR1 receptor antagonist with the ability to inhibit leukocyte activation and/or recruitment and thus expected to be useful in the prophylaxis or treatment of chronic inflammatory conditions including arthritis, atherosclerosis, ischemia/reperfusion injury, diabetes mellitus, psoriasis, multiple sclerosis, inflammatory bowel disease, organ and tissue transplant rejection, graft-versus-host disease, allergies and asthma. *In vitro*, compound gave an IC₅₀ of < 1 μM for inhibition of [¹²⁵I]-RANTES or [¹²⁵I]-MIP-1α binding in THP-1 cell membranes.

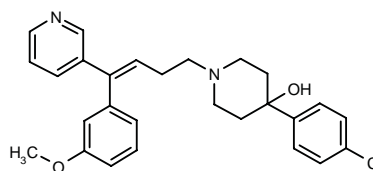
SOURCES – Kyowa Hakko; LeukoSite (Millennium).

REFERENCES

1. Luly, J.R. et al. (LeukoSite, Inc.;Kyowa Hakko Kogyo Co., Ltd.) *Chemokine receptor antagonists and methods of use therefor*. WO 0014089.

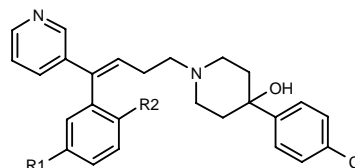
287223

4-(4-Chlorophenyl)-1-[4-(3-methoxyphenyl)-4-(3-pyridin-yl)-3-butenyl]piperidin-4-ol



C₂₇ H₂₉ Cl N₂ O₂; Mol wt: 448.9911

ACTION – Chemokine CCR1 receptor antagonist with the ability to inhibit leukocyte activation and/or recruitment and thus expected to be useful in the prophylaxis or treatment of chronic inflammatory conditions including arthritis, atherosclerosis, ischemia/reperfusion injury, diabetes mellitus, psoriasis, multiple sclerosis, inflammatory bowel disease, organ and tissue transplant rejection, graft-versus-host disease, allergies and asthma. *In vitro*, compound gave an IC₅₀ of < 1 μM for inhibition of [¹²⁵I]-RANTES or [¹²⁵I]-MIP-1α binding in THP-1 cell membranes. Other exemplified compounds include the following:



Compound	R1=R2	Isomer	Formula
287225	H		C ₂₆ H ₂₇ ClN ₂ O
287226	OMe	E	C ₂₈ H ₃₁ ClN ₂ O ₃

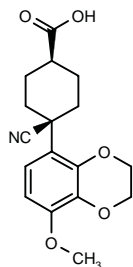
SOURCES – Kyowa Hakko; LeukoSite (Millennium).

REFERENCES

1. Luly, J.R. et al. (LeukoSite, Inc.;Kyowa Hakko Kogyo Co., Ltd.) *Chemokine receptor antagonists and methods of use therefor*. WO 0014086.

287321

cis-4-Cyano-4-(8-methoxy-2,3-dihydro-1,4-benzodioxin-5-yl)cyclohexanecarboxylic acid



C₁₇ H₁₉ N O₅; Mol wt: 317.3391

ACTION – Heterocyclic compound with phosphodiesterase type 4 (PDE4)-inhibitory activity (87% inhibition of recombinant human PDE4 activity at 1 μM).

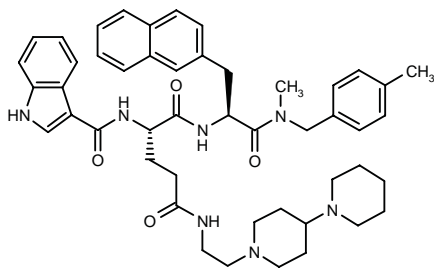
SOURCE – Kyowa Hakko.

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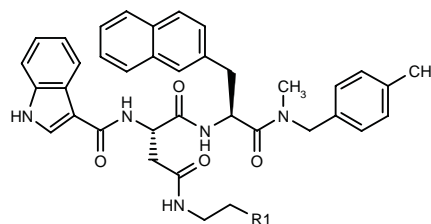
287505

*N*²-(1*H*-Indol-3-ylcarbonyl)-*N*⁵-[2-[4-(piperidin-1-yl)-piperidin-1-yl]ethyl]-L-glutaminy-L-(2-naphthyl)alanine *N*-methyl-*N*-(4-methylbenzyl)amide



C₄₈ H₅₉ N₇ O₄; Mol wt: 798.0391

ACTION – Tachykinin NK₁ receptor antagonist (pK_i = 10.0) with high stability and water solubility (> 10 mg/ml), potentially useful in the treatment of disorders where the substance P receptor is involved, particularly inflammatory airways disorders such as asthma and rhinitis, as well as conjunctivitis, dermatitis, psoriasis, ulcerative colitis, Crohn's disease and chemotherapy-induced emesis. *In vivo*, compound is reported to inhibit bronchospasm in guinea pigs following both i.v. and oral administration at low doses, and produced 79% inhibition of bronchial plasma protein extravasation induced by an NK₁ agonist in guinea pigs at 10 mg/kg p.o. Other compounds from this series containing an aromatic or aliphatic amino group include the following:



Compound	R1	Formula
287507	4-(1-Pip)-1-Pip	C ₄₇ H ₅₇ N ₇ O ₄
287508	4-Me-1-Piz-CH ₂	C ₄₄ H ₅₂ N ₆ O ₄

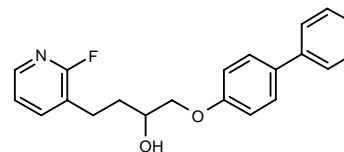
SOURCE – Menarini.

REFERENCES

1. Gröger, K. and Sisto, A. *Basic products having antagonistic activity on the NK-1 receptor and their use in pharmaceutical compsns.* WO 0014109.

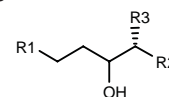
287666

(±)-1-(Biphenyl-4-yloxy)-4-(2-fluoropyridin-3-yl)butan-2-ol



C₂₁ H₂₀ F N O₂; Mol wt: 337.3920

ACTION – Modulator of inflammatory and allergic diseases that inhibits the activation of hematopoietic cells including mast cells, neutrophils and eosinophils. It was found to inhibit superoxide production from neutrophils in experimental assays. Potentially useful in the treatment of reversible obstructive airways disease, most particularly asthma, and especially the treatment and prophylaxis of asthma and rhinitis. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
287667	3-MeO-4-Pyr	4-Ph-PhO	H	C ₂₂ H ₂₃ NO ₃
287669	2-(MeNHCO)-Ph	2-Naph-S	H	C ₂₂ H ₂₃ NO ₂ S
287674	2-(MeNHCH ₂)-Ph	5,6,7,8-tetrahydro-2-Naph-O	H	C ₂₂ H ₂₉ NO ₂
287675	2-thiazolyl	4-(3-CN-Ph)-PhO	Me	C ₂₂ H ₂₁ NO ₂ S
287676	1-Me-5-oxo-3-pyrrolidinyl	4-Ph-PhO	H	C ₂₁ H ₂₅ NO ₃

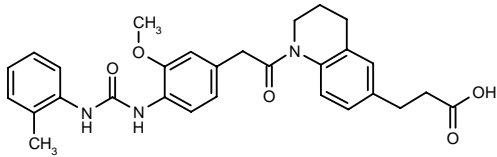
SOURCE – AstraZeneca.

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1. Cheshire, D. et al. (Astra Pharmaceuticals, Ltd.; Astra AB) *Novel cpds.* WO 0015614.

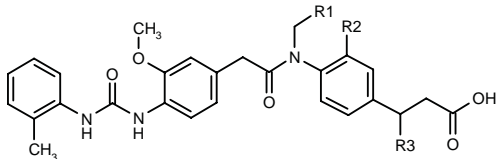
287678

3-[1-[2-[3-Methoxy-4-[3-(2-methylphenyl)ureido]-phenyl]acetyl]-1,2,3,4-tetrahydroquinolin-6-yl]propionic acid

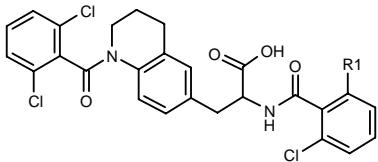


C29 H31 N3 O5; Mol wt: 501.5799

ACTION – Cell adhesion inhibitor that regulates the interaction of VCAM-1 and fibronectin with the integrin VLA-4 ($\alpha_4\beta_1$). Expected to be useful in the treatment or prevention of inflammatory diseases, specifically for asthma therapy. Other exemplified azabicyclic compounds include the following:



Compound	R1,R2	R3	Formula
287679	-CH2-	Me	C ₂₉ H ₃₁ N ₃ O ₅
287681	-(CH2)2-	Me	C ₃₀ H ₃₃ N ₃ O ₅
287682	-CH2-	CH2CO2H	C ₃₀ H ₃₁ N ₃ O ₇
287683	-(CH2)2-	CH2CO2H	C ₃₁ H ₃₅ N ₃ O ₅
287684	-(CH2)2-	NHCO(CH2)3CO2H	C ₃₄ H ₃₈ N ₄ O ₈
287685	-(CH2)2-	NHCOCH2CH2CO2H	C ₃₃ H ₃₆ N ₄ O ₈
287686	-(CH2)2-	5-Me-3-isoxazolyl-CONH	C ₃₄ H ₃₅ N ₅ O ₇
287689	-CH2-	Ph	C ₃₄ H ₃₃ N ₃ O ₅
287690	-CH2-	Et	C ₃₀ H ₃₃ N ₃ O ₅



Compound	R1	Formula
287687	Me	C ₂₇ H ₂₃ Cl ₃ N ₂ O ₄
287688	Cl	C ₂₆ H ₂₀ Cl ₄ N ₂ O ₄

SOURCE – Aventis Pharma.

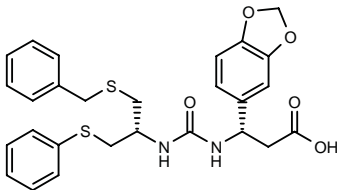
REFERENCES

1. Bourzat, J.-D. et al. (Rhône-Poulenc Rorer Ltd.) *Aza-bicycles which modulate the inhibition of cell adhesion*. WO 0015612.

TBC-3342

287441

3(S)-(1,3-Benzodioxol-5-yl)-3-[3-[2-(benzylsulfanyl)-1(S)-(phenylsulfanylmethyl)ethyl]ureido]propionic acid



C27 H28 N2 O5 S2; Mol wt: 524.6592

ACTION – Potent and selective VLA-4 antagonist from a series of urea analogues with an IC₅₀ of 20 nM in an $\alpha_4\beta_1$ /CS-1 binding assay. Potentially useful for the treatment of inflammatory diseases.

SOURCE – Texas Biotechnology.

REFERENCES

1. Kassir, J.M. et al. (Texas Biotechnology Corp.) *N,N-Disubst. amides that inhibit the binding of integrins to their receptors*. WO 9952493, WO 9952898.

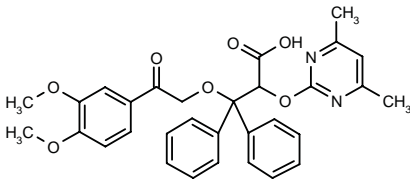
2. Biediger, R.J. et al. *Novel urea analogs that are potent VLA-4 antagonists*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 283.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

286643

3-[2-(3,4-Dimethoxyphenyl)-2-oxoethoxy]-2-(4,6-dimethyl-2-pyrimidinyl)-3,3-diphenylpropionic acid

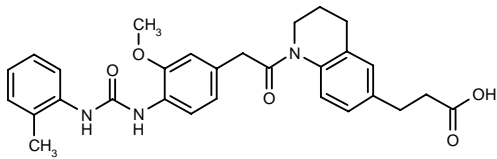


C31 H30 N2 O7; Mol wt: 542.5850

ACTION – Endothelin receptor antagonist that displays high affinity for ET_A receptors, giving a K_i value of 1.3 nM for ET_A receptors and of 21 nM for ET_B receptors. Potentially useful in the treatment of hypertension, chronic heart failure, restenosis, pulmonary hypertension, acute and chronic renal disease, cerebral ischemia and benign prostatic hyperplasia. Other exemplified carboxylic acid derivatives with keto side-chains include the following:

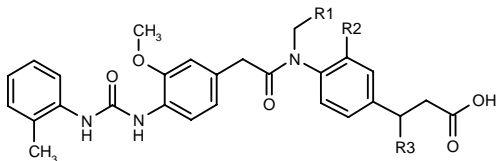
287678

3-[1-[2-[3-Methoxy-4-[3-(2-methylphenyl)ureido]-phenyl]acetyl]-1,2,3,4-tetrahydroquinolin-6-yl]propionic acid

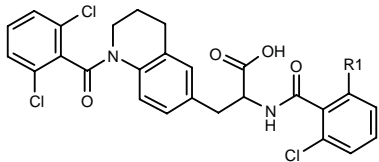


C29 H31 N3 O5; Mol wt: 501.5799

ACTION – Cell adhesion inhibitor that regulates the interaction of VCAM-1 and fibronectin with the integrin VLA-4 ($\alpha_4\beta_1$). Expected to be useful in the treatment or prevention of inflammatory diseases, specifically for asthma therapy. Other exemplified azabicyclic compounds include the following:



Compound	R1,R2	R3	Formula
287679	-CH2-	Me	C ₂₉ H ₃₁ N ₃ O ₅
287681	-(CH2)2-	Me	C ₃₀ H ₃₃ N ₃ O ₅
287682	-CH2-	CH2CO2H	C ₃₀ H ₃₁ N ₃ O ₇
287683	-(CH2)2-	CH2CO2H	C ₃₁ H ₃₅ N ₃ O ₅
287684	-(CH2)2-	NHCO(CH2)3CO2H	C ₃₄ H ₃₈ N ₄ O ₈
287685	-(CH2)2-	NHCOCH2CH2CO2H	C ₃₃ H ₃₆ N ₄ O ₈
287686	-(CH2)2-	5-Me-3-isoxazolyl-CONH	C ₃₄ H ₃₅ N ₅ O ₇
287689	-CH2-	Ph	C ₃₄ H ₃₃ N ₃ O ₅
287690	-CH2-	Et	C ₃₀ H ₃₃ N ₃ O ₅



Compound	R1	Formula
287687	Me	C ₂₇ H ₂₃ Cl ₃ N ₂ O ₄
287688	Cl	C ₂₆ H ₂₀ Cl ₄ N ₂ O ₄

SOURCE – Aventis Pharma.

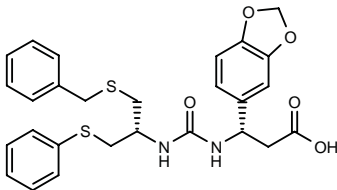
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1. Bourzat, J.-D. et al. (Rhône-Poulenc Rorer Ltd.) *Aza-bicycles which modulate the inhibition of cell adhesion*. WO 0015612.

TBC-3342

287441

3(S)-(1,3-Benzodioxol-5-yl)-3-[3-[2-(benzylsulfanyl)-1(S)-(phenylsulfanylmethyl)ethyl]ureido]propionic acid



C27 H28 N2 O5 S2; Mol wt: 524.6592

ACTION – Potent and selective VLA-4 antagonist from a series of urea analogues with an IC₅₀ of 20 nM in an $\alpha_4\beta_1$ /CS-1 binding assay. Potentially useful for the treatment of inflammatory diseases.

SOURCE – Texas Biotechnology.

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1. Kassir, J.M. et al. (Texas Biotechnology Corp.) *N,N-Disubst. amides that inhibit the binding of integrins to their receptors*. WO 9952493, WO 9952898.

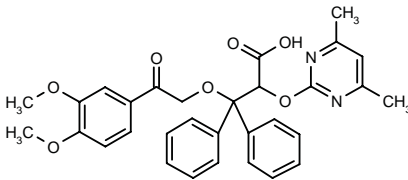
2. Biediger, R.J. et al. *Novel urea analogs that are potent VLA-4 antagonists*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 283.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

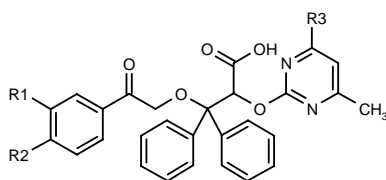
286643

3-[2-(3,4-Dimethoxyphenyl)-2-oxoethoxy]-2-(4,6-dimethyl-2-pyrimidinyl)-3,3-diphenylpropionic acid



C31 H30 N2 O7; Mol wt: 542.5850

ACTION – Endothelin receptor antagonist that displays high affinity for ET_A receptors, giving a K_i value of 1.3 nM for ET_A receptors and of 21 nM for ET_B receptors. Potentially useful in the treatment of hypertension, chronic heart failure, restenosis, pulmonary hypertension, acute and chronic renal disease, cerebral ischemia and benign prostatic hyperplasia. Other exemplified carboxylic acid derivatives with keto side-chains include the following:



Compound	R1	R2	R3	Formula
286644	OMe	OMe	OMe	C ₃₁ H ₃₀ N ₂ O ₈
286645	H	H	OMe	C ₂₉ H ₂₈ N ₂ O ₆
286646	H	H	Me	C ₂₉ H ₂₈ N ₂ O ₅
286647	H	Br	Me	C ₂₉ H ₂₅ BrN ₂ O ₅
286648	H	Br	OMe	C ₂₉ H ₂₅ BrN ₂ O ₆

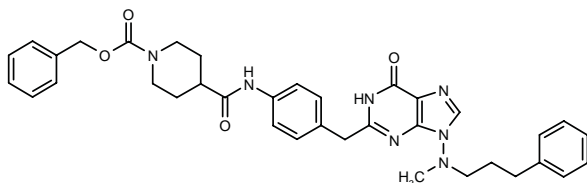
SOURCE – BASE.

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1. Amberg, W. et al. (BASF AG) *New carboxylic acid derivs. carrying keto side-chains, their production and their use as endothelin-receptor antagonists*. DE 19836044, WO 0009489.

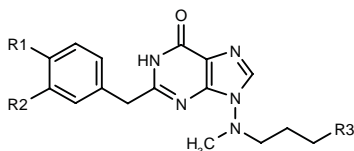
286767

4-[N-[4-[9-[N-Methyl-N-(3-phenylpropyl)amino]-hypoxanthin-2-ylmethyl]phenyl]carbamoyl]piperidine-1-carboxylic acid benzyl ester



C36 H39 N7 O4; Mol wt: 633.7491

ACTION – Agent for the treatment of cardiovascular diseases such as hypertension and angina, as well as peripheral vascular diseases and diseases of the urogenital tract, an inhibitor of cGMP-phosphodiesterases (PDE) with selectivity for PDE2 ($IC_{50} = 50$ nM) over PDE1 ($IC_{50} = 300$ nM) and PDE5 ($IC_{50} > 1000$ nM). Other compounds from this series of 9-dialkylamino purinone derivatives include the following:



Compound	R1	R2	R3	Formula
286768	1-(PhCH ₂ OCO)-4-Pip-CONH	H	Pr	C ₃₃ H ₄₁ N ₇ O ₄
286769	OMe	OMe	Ph	C ₂₄ H ₂₇ N ₅ O ₃
286770	4-Me-1-Piz-SO ₂	H	Ph	C ₂₇ H ₃₃ N ₇ O ₃ S

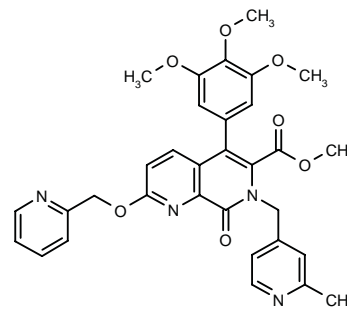
SOURCE – Bayer.

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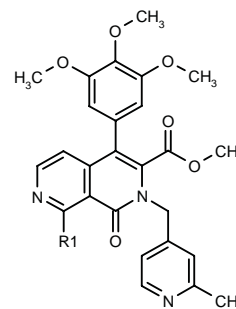
287227

7-(2-Methylpyridin-4-ylmethyl)-8-oxo-2-(2-pyridinylmethoxy)-5-(3,4,5-trimethoxyphenyl)-7,8-dihydro-1,7-naphthyridine-6-carboxylic acid methyl ester

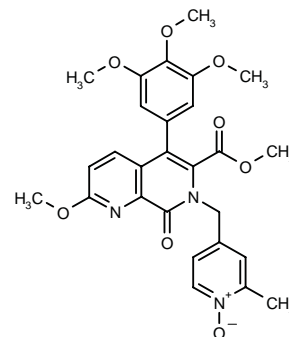


C32 H30 N4 O7; Mol wt: 582.6100

ACTION – Agent for the treatment of circulatory disorders with excellent inhibitory activity against phosphodiesterase type 5 (PDE5). Other specifically claimed compounds from this series of naphthyridine derivatives include the following:



Compound	R1	Formula
287229	2-pyrimidinyl-CH ₂ O	C ₃₁ H ₂₉ N ₅ O ₇
287232	2-Pyr-CH ₂ NH	C ₃₂ H ₃₁ N ₅ O ₆
287236	1-Me-2-imidazolyl-CH ₂ O	C ₃₁ H ₃₁ N ₅ O ₇
287237	5-oxo-2-pyrrolidinyl-CH ₂ O	C ₃₁ H ₃₂ N ₄ O ₈
287238	2(S)-pyrrolidinyl-CH ₂ O	C ₃₁ H ₃₄ N ₄ O ₇



287235: C27 H27 N3 O8

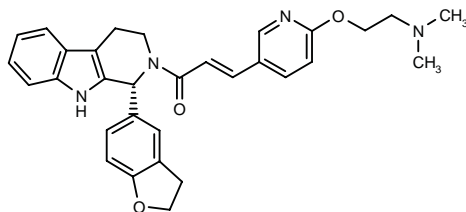
SOURCE – Tanabe Seiyaku.

REFERENCES

1. Ukita, T. et al. (Tanabe Seiyaku Co., Ltd.) *Naphthyridine derivs. and process for the preparation thereof*. WO 0012503.

287568

1-[1 (*R*)-(2,3-Dihydro-1-benzofuran-5-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-2-yl]-3-[6-[2-(dimethylamino)ethoxy]pyridin-3-yl]-2(*E*)-propen-1-one



C31 H32 N4 O3; Mol wt: 508.6188

ACTION – Agent for the treatment of cardiovascular disorders and erectile dysfunction, a potent and selective inhibitor of cGMP phosphodiesterase type 5 (PDE5; IC_{50} = 10 nM against recombinant human enzyme). Compound was also shown to stimulate guanylate cyclase activity in rat aortic smooth muscle cells with an EC_{50} < 1 μ M and it displayed potent blood pressure-lowering effects in conscious spontaneously hypertensive rats following oral administration at a dose of 5 mg/kg. A specifically claimed compound from a series of carboline derivatives.

SOURCE – Icos.

REFERENCES

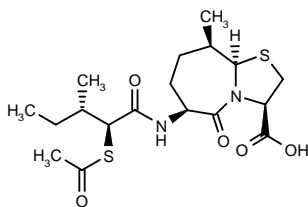
1. Bombrun, A. and Gellibert, F. (ICOS Corp.) *Carboline derivs. as cGMP phosphodiesterase inhibitors*. WO 0015639.

E-4030¹⁻⁷

283794

(3*R*,6*S*,9*R*,9*aR*)-6-[2(*S*)-(Acetylsulfanyl)-3(*S*)-methylpentanamido]-9-methyl-5-oxooctahydrothiazolo[3,2-*a*]azepine-3-carboxylic acid

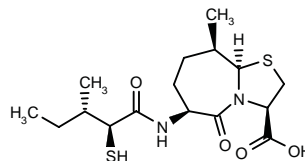
ER-40133



C18 H28 N2 O5 S2; Mol wt: 416.5602

ACTION – Antihypertensive agent, an oral prodrug of **ER-40121** which is a potent dual inhibitor of angiotensin-converting enzyme (ACE; IC_{50} = 2.3 nM against enzyme from rat lung) and neutral endopeptidase (NEP; IC_{50} = 1.4 nM against enzyme from rat kidney). Pharmacokinetic studies in dogs demonstrated that the prodrug is orally bioavailable (74-94% at doses of 0.33-3.33 mg/kg p.o.) and has a long duration of action (mean residence time = 4.9-5.9 h at doses of 0.33-3.33 mg/kg p.o.). Significant antihypertensive effects were demonstrated in both DOCA-salt hypertensive rats, where compound given orally (30 mg/kg p.o.) effectively reduced blood pressure

(37% decrease at 9 h after administration) and in 2-kidney, 1-clip Goldblatt hypertensive dogs, where at doses of 1-3 mg/kg p.o. it produced a similar effect to enalapril. Potentially useful for the treatment of cardiovascular diseases such as hypertension and congestive heart failure.



ER-40121 [237707]^{*1,2,6}: C16 H26 N2 O4 S2

SOURCE – Eisai.

REFERENCES

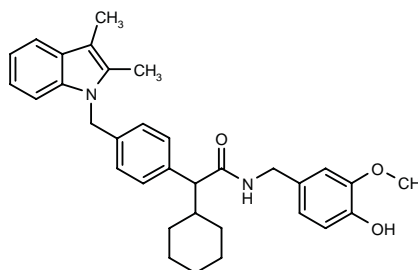
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3. Sudo, T. et al. (Eisai Co., Ltd.) *Cholesterol-lowering compsn.* WO 9717972.
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7. Torisuka, N. et al. *Mechanism of weight gain suppressing effect of ER-40133, an angiotensin I converting enzyme inhibitor, in growing rats*. J Toxicol Sci 1999, 24(1): 45.

*Identified compound **237707** (see **235140**) Drug Data Rep 1996, 018(07): 0606.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

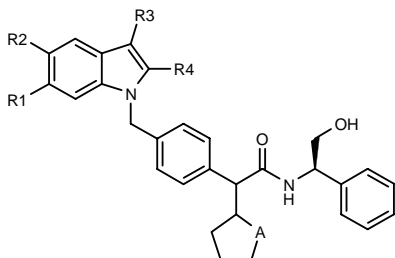
286681

2-Cyclohexyl-*N*-(4-hydroxy-3-methoxybenzyl)-2-[4-(2,3-dimethyl-1*H*-indol-1-ylmethyl)phenyl]acetamide enantiomer A

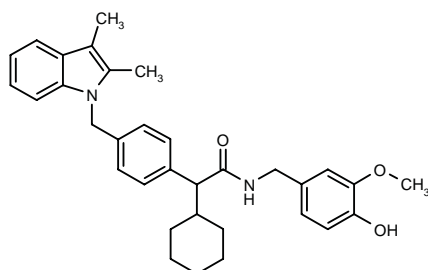


C33 H38 N2 O3; Mol wt: 510.6742

ACTION – Antiatherosclerotic agent that inhibits smooth muscle cell proliferation and the release of apolipoprotein B-100 (ApoB-100)-associated lipoproteins such as VLDL. *In vitro*, compound was shown to inhibit the release of ApoB-100-associated particles in cultured HepG2 cells with an IC_{50} value of 10.8 nM. *In vivo*, it significantly reduced the postprandial increase in serum triglycerides in rats with an ED_{50} value of < 3 mg/kg p.o. Other compounds from this series of indolyl-substituted phenylacetic acid derivatives include the following:



Compound	R1	R2	R3	R4	A	Isomer	Formula
286682	H	H	Me	Me	-(CH ₂) ₃ -		C ₃₄ H ₄₀ N ₂ O ₂
286684	H	OMe	H	CO ₂ Et	-CH ₂ -		C ₃₄ H ₃₈ N ₂ O ₅
286685	H	H	Me	H	-(CH ₂) ₃ -		C ₃₃ H ₃₈ N ₂ O ₂
286686	Cl	H	H	H	-CH ₂ -	A	C ₃₀ H ₃₁ ClN ₂ O ₂



286683: C₃₃ H₃₈ N₂ O₃

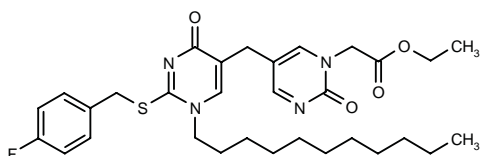
SOURCE – Bayer.

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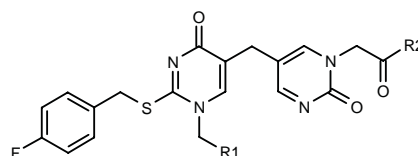
286943

2-[5-[2-(4-Fluorobenzylsulfanyl)-4-oxo-1-undecyl-1,4-dihydropyrimidin-5-ylmethyl]-2-oxo-1,2-dihydropyrimidin-1-yl]acetic acid ethyl ester



C₃₁ H₄₁ F N₄ O₄ S; Mol wt: 584.7529

ACTION – An inhibitor of lipoprotein-associated phospholipase A₂ (Lp-PLA₂) with potential in the treatment of atherosclerosis, as well as diabetes, hypertension, angina pectoris and ischemia/reperfusion injury. Other specifically claimed compounds from this series of pyrimidinone derivatives include the following:



Compound	R1	R2	Formula
286944	H	OEt	C ₂₁ H ₂₁ FN ₄ O ₄ S
286945	H	N(Me)CH ₂ Ph	C ₂₇ H ₂₈ FN ₅ O ₃ S
286946	H	4-OH-4-(PhCH ₂)-1-Pip	C ₃₁ H ₃₂ FN ₅ O ₄ S
286947	CON(Me)C ₈ H ₁₇	OH	C ₂₉ H ₃₆ FN ₅ O ₅ S
286948	CON(Me)C ₈ H ₁₇	NHMe	C ₃₀ H ₃₉ FN ₆ O ₄ S
286949	CON(Me)C ₁₂ H ₂₅	ONa	C ₃₃ H ₄₃ FN ₆ NaO ₅ S

SOURCE – SmithKline Beecham.

REFERENCES

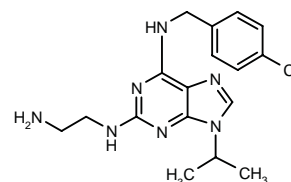
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CVT-2584

286968

*N*²-(2-Aminoethyl)-*N*⁶-(4-chlorobenzyl)-9-isopropyl-9*H*-purine-2,6-diamine

N-(2-Aminoethyl)-*N*-[6-(4-chlorobenzylamino)-9-isopropyl-9*H*-purin-2-yl]amine



C₁₇ H₂₂ Cl N₇; Mol wt: 359.8628

ACTION – Cyclin-dependent kinase 2 (CDK2) inhibitor (IC_{50} = 0.27 μ M) with selectivity relative to CDK1 (IC_{50} = 10.3 μ M), proven to inhibit vascular smooth muscle proliferation with an IC_{50} of 0.28 μ M. Reported to reduce neointimal thickening in a rat model of restenosis. Potentially useful for the treatment of restenosis after angioplasty.

SOURCE – CV Therapeutics.

REFERENCES

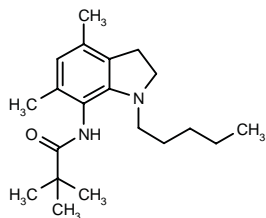
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KY-455

235420

N-(4,6-Dimethyl-1-pentyl-2,3-dihydro-1*H*-indol-7-yl)-2,2-dimethylpropionamide



C20 H32 N2 O; Mol wt: 316.4858

ACTION – ACAT inhibitor and antioxidant, as demonstrated by its ability to competitively inhibit ACAT activity from hypercholesterolemic rabbit intestinal mucosa, liver and aorta at 0.01-1 μ M and LDL peroxidation at 0.1-10 μ M. In rabbits fed a high-cholesterol diet, a dose of 30 mg/kg/day p.o. for 8 days completely inhibited the increase in plasma total cholesterol and strongly reduced serum LDL cholesterol, hepatic total cholesterol and esterified and free cholesterol, without affecting serum HDL cholesterol. The compound also inhibited hepatic ACAT activity and the peroxidation of rabbit plasma *ex vivo*. Potentially useful for the treatment of atherosclerosis.

SOURCE – Kyoto Pharmaceutical.

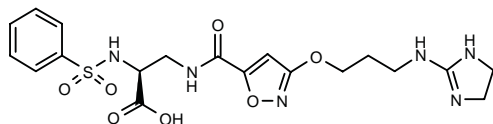
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6. Yamaguchi, Y. et al. *Preventive effect of KY-455, a new ACAT inhibitor, on oxidative modification of LDL*. Jpn J Pharmacol 2000, 82(Suppl. 1): Abst P-369.

XT-199

286400

3-[3-[3-(4,5-Dihydro-1*H*-imidazol-2-ylamino)propoxy]-isoxazol-5-ylcarboxamido]-2(*S*)-(phenylsulfonamido)-propionic acid



C19 H24 N6 O7 S; Mol wt: 480.4996

ACTION – Selective, nonpeptide antagonist of the vitronectin ($\alpha_v\beta_3$ integrin) receptor ($IC_{50} = 0.05$ and $> 10 \mu$ M, respectively, against $\alpha_v\beta_3$ and gpIIb/IIIa) proven to reduce restenosis and macrophage infiltration in atherosclerotic rabbits after balloon angioplasty; in this model, animals treated at doses of 2.5 mg/kg by i.v. bolus plus 2.5 mg/kg/day i.v. by osmotic pump for 14 days showed a significantly larger lumen and smaller intimal area than control animals. In addition, in the same model compound produced a reduction in restenosis (30-40%) and in intimal-medial ICAM-1 expression. Compound also showed potent antiangiogenic activity in a mouse matrigel model of angiogenesis ($ED_{50} = 45 \mu$ g/kg/day s.c. infused for 7 days) and was shown to reduce by 20% the growth of human colon carcinoma RKO xenografts in mice. Potentially useful for the treatment of restenosis after balloon angioplasty and other angiogenesis-mediated disorders including tumor growth and metastasis.

SOURCE – DuPont Pharmaceuticals.

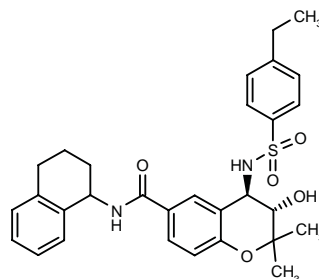
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ANTIARRHYTHMIC DRUGS

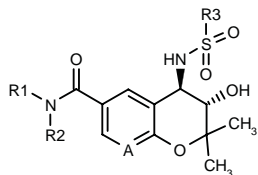
287195

trans-4-(4-Ethylphenylsulfonamido)-3-hydroxy-2,2-dimethyl-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-3,4-dihydro-2*H*-1-benzopyran-6-carboxamide

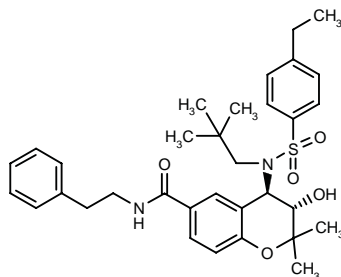


C30 H34 N2 O5 S; Mol wt: 534.6736

ACTION – Potassium channel inhibitor that blocks the delayed rectifier voltage-gated potassium channel termed IK_{ur} , reported to contain the voltage-gated potassium channel $Kv1.5$ α -subunit gene product, thought to be important in the repolarization of the human atrial action potential. This compound is thus useful in the treatment of cardiac arrhythmias, especially those occurring in the atria, as well as cell proliferative disorders, i.e., leukemia, and autoimmune diseases such as rheumatoid arthritis and transplant rejection. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	Formula
287196	H	4-Pyr-CH2CH2	4-Et-Ph	CH	C ₂₇ H ₃₁ N ₃ O ₅ S
287201	H	4-(2-furyl)-6-MeO-2-pyrimidinyl	4-Et-Ph	CH	C ₂₉ H ₃₀ N ₄ O ₇ S
287202	H	CH2CH2Ph	4-(CF3O)-Ph	CH	C ₂₇ H ₂₇ F ₃ N ₂ O ₆ S
287204	Et	1,3-benzodioxol-5-yl	4-Et-Ph	N	C ₂₈ H ₃₁ N ₃ O ₇ S
287206	Me	4-Pyr-CH2CH2	4-Et-Ph	CH	C ₂₈ H ₃₃ N ₃ O ₅ S
287208	Et	1-(PhCH2)-3-pyrrolidinyl	1-Naph	CH	C ₃₅ H ₃₉ N ₃ O ₅ S
287209	H	4-Br-Ph	2-MeO-5-Cl-Ph	CH	C ₂₅ H ₂₄ BrClN ₂ O ₆ S



287203: C₃₃ H₄₂ N₂ O₅ S

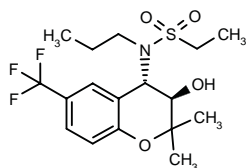
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Lloyd, J. et al. (Bristol-Myers Squibb Co.) *Potassium channel inhibitors and method.* WO 0012077.

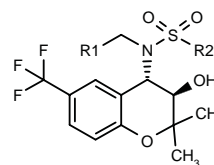
287314

N-[3(*R*)-Hydroxy-2,2-dimethyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-1-benzopyran-4(*S*)-yl]-*N*-propylethane-1-sulfonamide



C₁₇ H₂₄ F₃ N O₄ S; Mol wt: 395.4396

ACTION – Class III antiarrhythmic and antifibrillatory agent that acts primarily by blocking the $K_{V(s)}$ channel, reported to exhibit less side effects as compared to many conventional antiarrhythmic therapies. Compound is also reported to be of use in the treatment of diarrhea and ulcers. Other specifically claimed compounds from this series of substituted dihydrobenzopyrans include the following:



Compound	R1	R2	Formula
287315	Me	Et	C ₁₆ H ₂₂ F ₃ NO ₄ S
287316	H	Ph	C ₁₉ H ₂₀ F ₃ NO ₄ S
287317	H	Pr	C ₁₆ H ₂₂ F ₃ NO ₄ S
287318	H	i-Pr	C ₁₆ H ₂₂ F ₃ NO ₄ S
287319	H	Me	C ₁₄ H ₁₈ F ₃ NO ₄ S

SOURCE – Procter & Gamble.

REFERENCES

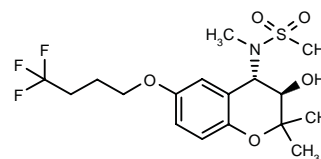
1. Scherz, M.W. (The Procter & Gamble Co.) *Substd. dihydrobenzopyrans useful as antiarrhythmic agents.* WO 0014084.

HMR-1556*

276302

(+)-*N*-[2,2-Dimethyl-3(*R*)-hydroxy-6-(4,4,4-trifluorobutoxy)-3,4-dihydro-2*H*-1-benzopyran-4(*S*)-yl]-*N*-methylmethanesulfonamide

(+)-*N*-[2,2-Dimethyl-3(*R*)-hydroxy-6-(4,4,4-trifluorobutoxy)chroman-4(*S*)-yl]-*N*-methylmethanesulfonamide



C₁₇ H₂₄ F₃ N O₅ S; Mol wt: 411.4386

ACTION – Potent and selective $K_{V(s)}$ channel blocker (IC_{50} = 34 nM), selected for further study as a potential antiarrhythmic agent.

SOURCE – Aventis Pharma.

REFERENCES

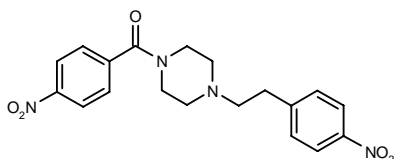
1. Brendel, J. et al. (Aventis Pharma Deutschland GmbH) *Sulphonamide substd. benzopyran derivs., process of preparation, their use as medicines and pharmaceutical compns. containing them.* CA 2252733, DE 19748469, EP 0913396, JP 1999222485, US 6008245.

2. Brendel, J. et al. *Synthesis and SAR of a novel IKS-channel blockers: From K(ATP)-channel opener to IKS-channel blocker.* 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 159.

*Identified compound **276302** (see **276294**) Drug Data Rep 1999, 021(09): 0790.

RWJ-28810**287072**

[4-[2-(4-Nitrophenyl)ethyl]piperazin-1-yl](4-nitrophenyl)-methanone



C₁₉ H₂₀ N₄ O₅; Mol wt: 384.3900

ACTION – Potent and selective class III antiarrhythmic agent proven to prolong the effective refractory period in ferret papillary muscle with an EC₂₀ of 3 nM, being about 50 times more potent than the reference compound UK-68798.

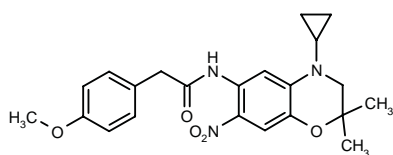
SOURCE – R.W. Johnson.

REFERENCES

1. Kanojia, R.M. et al. *Synthesis and selective class III type antiarrhythmic activity of 4-aryloxy (and aryloxy)-1-alkylpiperazines*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 204.

HEART FAILURE THERAPY
286962

N-(4-Cyclopropyl-2,2-dimethyl-7-nitro-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)-2-(4-methoxyphenyl)acetamide



C₂₂ H₂₅ N₃ O₅; Mol wt: 411.4555

ACTION – Bradycardic agent for the treatment of heart failure, reported to reduce heart rate in guinea pig right atrial preparations in a concentration-dependent manner at 10-300 µM. A representative compound from a series of benzoxazine derivatives.

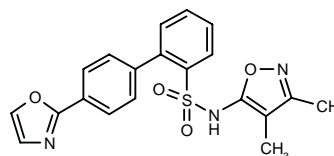
SOURCE – Nissan Chemical.

REFERENCES

1. Tanikawa, K. et al. (Nissan Chemical Industry, Ltd.) *Benzoxazine derivs*. WO 0012492.

BMS-193884***235874**

N-(3,4-Dimethylisoxazol-5-yl)-4'-(2-oxazolyl)biphenyl-2-sulfonamide



C₂₀ H₁₇ N₃ O₄ S; Mol wt: 395.4400

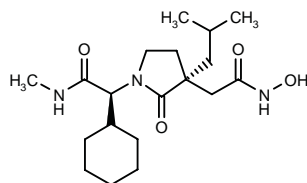
ACTION – Potent and selective endothelin ET_A receptor antagonist with a K_i value of 1.4 nM for ET_A receptors versus 1900 nM for ET_B receptors. In a preclinical model of congestive heart failure in pigs, compound was shown to improve left ventricular pump function, to reduce sympathetic activity and to protect myocytes from contractile dysfunction, without reducing systemic blood pressure. It has an oral bioavailability of 95%. Phase II clinical trials in heart failure patients demonstrated favorable hemodynamic effects and good tolerance. Potentially useful for the treatment of congestive heart failure.

SOURCE – Bristol-Myers Squibb.

REFERENCES

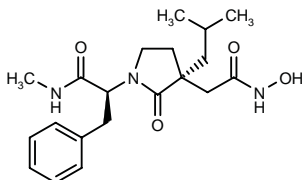
1. Bird, J.E. (Bristol-Myers Squibb Co.) *Method for preventing or treating low renin hypertension by administering an endothelin antagonist*. WO 9833781.
2. Murugesan, N. et al. (Bristol-Myers Squibb Co.) *Substd. biphenyl isoxazole sulfonamides*. EP 0921800, US 5846990, WO 9729748.
3. Murugesan, N. and Barrish, J.C. (Bristol-Myers Squibb Co.) *Substd. isoxazole sulfonamides and their use as endothelin antagonists*. CA 2155447, EP 0702012, JP 1996183786.
4. Rajfer, S.I. (Bristol-Myers Squibb Co.) *Method for preventing or treating erectile dysfunction by administering an endothelin antagonist*. WO 9910345.
5. Miyauchi, T. et al. *Contribution of endogenous endothelin-1 to the progression of right-sided heart failure caused by pulmonary hypertension in rats: Improvement of survival and of failing right ventricular gene expression by chronic treatment*. Circulation 1999, 100(18, Suppl. 1): Abst 1419.
6. Murugesan, N. *The discovery of BMS-193884, a potent and selective ET_A receptor antagonist*. 6th Int Conf Endothelin (Oct 10-13, Montreal) 1999, Abst 021.
7. Murugesan, N. et al. *Discovery of BMS-193884, a potent and selective ET_A receptor antagonist*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 164.
8. Phillips, P.A. *Interaction between endothelin and angiotensin II*. Clin Exp Pharmacol Physiol 1999, 26(7): 517.
9. Saad, D. et al. *Endothelin subtype-A receptor blockade prevents the progression of left ventricular and myocyte contractile dysfunction with developing congestive heart failure*. Circulation 1998, 98(17, Suppl.): Abst 3779.
10. Saad, D. et al. *The effects of endothelin-A receptor blockade during the progression of pacing-induced congestive heart failure*. J Am Coll Cardiol 1998, 32(6): 1779.
11. Smith, W. et al. *Improved hemodynamics with the ET_A selective receptor antagonists BMS-193884 in patients with heart failure*. J Am Coll Cardiol 2000, 35(2, Suppl. A): 241A.
12. Strachan, F. et al. *Local and systemic vasodilatation in healthy volunteers in vivo with the ET_A selective antagonist, BMS193884*. 6th Int Conf Endothelin (Oct 10-13, Montreal) 1999, Abst 217.
13. *Orally active ET antagonist from BMS in clinical trials*. DailyDrugNews.com (Daily Essentials) 1997, July 18.
14. Bristol-Myers Squibb Co. Annual Report 1995.

*Identified compound **235874** (see **235172**) Drug Data Rep 1996, 018(06): 0521.

PNU-171829¹⁻³**282121**2-[1-[1(*S*)-Cyclohexyl-1-(*N*-methylcarbamoyl)methyl]-3(*S*)-isobutyl-2-oxopyrrolidin-3-yl]acetohydroxamic acid

C19 H33 N3 O4; Mol wt: 367.4867

ACTION – Potent matrix metalloproteinase inhibitor ($K_i = 15$ and 18 nM against gelatinase and interstitial collagenase, respectively) proven to improve heart systolic function and attenuate cardiac hypertrophy without affecting late ventricular remodeling when administered at a dose of 150 mg/kg/day s.c. for 4 weeks to rats with experimental heart failure. Selected as a clinical candidate for the treatment of a number of diseases including cancer, arthritis and congestive heart failure. Within this series of lactam hydroxamates, the following is also included:

**PNU-109849 [286881]^{1,3}**: C20 H29 N3 O4**SOURCE** – Pharmacia.**REFERENCES**

- Jacobsen, E.J. (Pharmacia & Upjohn AB) *Hydroxamic acid derivs. for use with the treatment of diseases related to connective tissue degradation*. EP 0898562, US 5712300, WO 9732846.
- Gurbanov, K.G. et al. *Effects of matrix metalloproteinase inhibitor, PNU171829, on heart function, late cardiac remodeling and hypertrophy in rats with experimental congestive heart failure*. Circulation 1999, 100(18, Suppl. 1): Abstr 3720.
- Hendges, S.K. et al. *Novel lactam hydroxamates as inhibitors of matrix metalloproteinases*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abstr MEDI 17.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

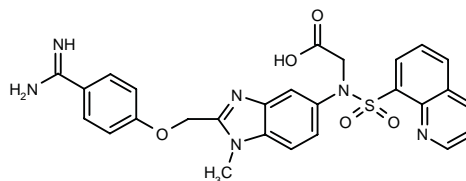
10C12**287091***Human anti-factor IX/IXa antibody*

ACTION – Human antibody to the γ -carboxyglutamic acid (Gla) domain of human factor IX and human factor IXa, with potential in the treatment or prevention of coagulation and thrombotic disorders such as deep venous

thrombosis, arterial thrombosis, unstable angina, postmyocardial infarction, stroke, PTCA (percutaneous transluminal coronary angioplasty), inflammation, tumor growth and metastasis, septic shock, hypotension, atrial fibrillation and disseminated intravascular coagulation (DIC), as well as for use as an adjunct in thrombolytic therapy. Compound exhibited potent affinity for human factor IX ($K_d = 1.6$ nM) and was found to inhibit the binding of factor IX to bovine aortic endothelial cells with an IC_{50} in the range $20-50$ nM. In addition, it was found to double the activated partial thromboplastin time (APTT) in human, guinea pig and rat plasma at concentrations of 60 , 65 and 60 μ g/ml, respectively. *In vivo*, it was effective in reducing clot weight and duration of vessel occlusion in an $FeCl_3$ -induced arterial thrombosis model in rats at 1000 μ g/kg i.v., being comparable in potency to heparin infusion at 1 U/kg/min.

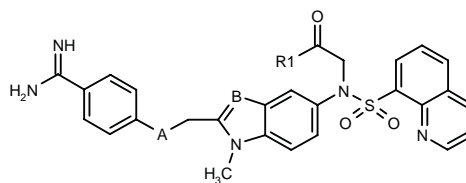
SOURCE – Genentech.**REFERENCES**

- Adams, C.W. et al. (Genentech, Inc.) *Human anti-factor IX/IXa antibodies*. WO 0012562.

2864212-[*N*-[2-(4-Amidinophenoxymethyl)-1-methyl-1*H*-benzimidazol-5-yl]-*N*-(8-quinolylsulfonyl)amino]acetic acid

C27 H24 N6 O5 S; Mol wt: 544.5896

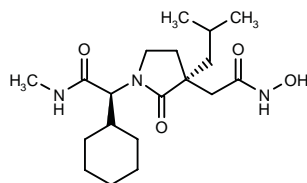
ACTION – Anticoagulant and antithrombotic agent, an inhibitor of thrombin also reported to inhibit other serine proteases. *In vitro*, compound was shown to double the thrombin time in human plasma at a concentration of 0.015 μ M. Other specifically claimed compounds from this series of disubstituted bicyclic heterocycles include the following:



Compound	R1	A	B	Formula
286422	NHCH2CO2H	CH2	N	C ₃₀ H ₂₉ N ₇ O ₅ S
286425	OH	NH	N	C ₂₇ H ₂₅ N ₇ O ₄ S
286426	OH	NH	CH	C ₂₈ H ₂₆ N ₆ O ₄ S

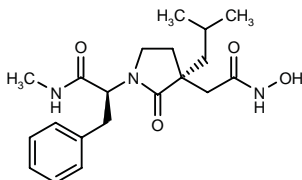
SOURCE – Boehringer Ingelheim.**REFERENCES**

- Hauel, N. et al. (Boehringer Ingelheim Pharma KG) *Disubstd. bicyclic heterocycles having, in particular, a thrombin inhibitive effect*. DE 19834751, WO 0008014.

PNU-171829¹⁻³**282121**2-[1-[1(*S*)-Cyclohexyl-1-(*N*-methylcarbamoyl)methyl]-3(*S*)-isobutyl-2-oxopyrrolidin-3-yl]acetohydroxamic acid

C19 H33 N3 O4; Mol wt: 367.4867

ACTION – Potent matrix metalloproteinase inhibitor ($K_i = 15$ and 18 nM against gelatinase and interstitial collagenase, respectively) proven to improve heart systolic function and attenuate cardiac hypertrophy without affecting late ventricular remodeling when administered at a dose of 150 mg/kg/day s.c. for 4 weeks to rats with experimental heart failure. Selected as a clinical candidate for the treatment of a number of diseases including cancer, arthritis and congestive heart failure. Within this series of lactam hydroxamates, the following is also included:

**PNU-109849 [286881]^{1,3}**: C20 H29 N3 O4**SOURCE** – Pharmacia.**REFERENCES**

- Jacobsen, E.J. (Pharmacia & Upjohn AB) *Hydroxamic acid derivs. for use with the treatment of diseases related to connective tissue degradation*. EP 0898562, US 5712300, WO 9732846.
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AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

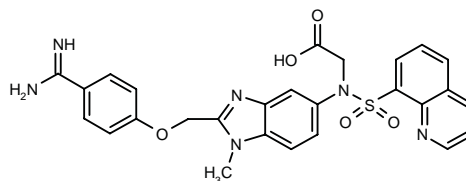
10C12**287091***Human anti-factor IX/IXa antibody*

ACTION – Human antibody to the γ -carboxyglutamic acid (Gla) domain of human factor IX and human factor IXa, with potential in the treatment or prevention of coagulation and thrombotic disorders such as deep venous

thrombosis, arterial thrombosis, unstable angina, postmyocardial infarction, stroke, PTCA (percutaneous transluminal coronary angioplasty), inflammation, tumor growth and metastasis, septic shock, hypotension, atrial fibrillation and disseminated intravascular coagulation (DIC), as well as for use as an adjunct in thrombolytic therapy. Compound exhibited potent affinity for human factor IX ($K_d = 1.6$ nM) and was found to inhibit the binding of factor IX to bovine aortic endothelial cells with an IC_{50} in the range 20 - 50 nM. In addition, it was found to double the activated partial thromboplastin time (APTT) in human, guinea pig and rat plasma at concentrations of 60 , 65 and 60 μ g/ml, respectively. *In vivo*, it was effective in reducing clot weight and duration of vessel occlusion in an $FeCl_3$ -induced arterial thrombosis model in rats at 1000 μ g/kg i.v., being comparable in potency to heparin infusion at 1 U/kg/min.

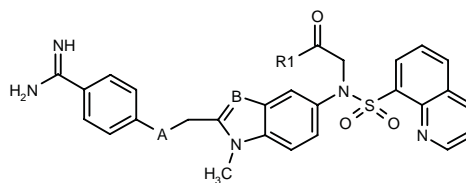
SOURCE – Genentech.**REFERENCES**

- Adams, C.W. et al. (Genentech, Inc.) *Human anti-factor IX/IXa antibodies*. WO 0012562.

2864212-[*N*-[2-(4-Amidinophenoxymethyl)-1-methyl-1*H*-benzimidazol-5-yl]-*N*-(8-quinolinylsulfonyl)amino]acetic acid

C27 H24 N6 O5 S; Mol wt: 544.5896

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of thrombin also reported to inhibit other serine proteases. *In vitro*, compound was shown to double the thrombin time in human plasma at a concentration of 0.015 μ M. Other specifically claimed compounds from this series of disubstituted bicyclic heterocycles include the following:



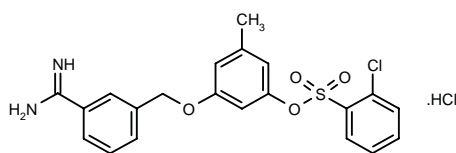
Compound	R1	A	B	Formula
286422	NHCH2CO2H	CH2	N	C ₃₀ H ₂₉ N ₇ O ₅ S
286425	OH	NH	N	C ₂₇ H ₂₅ N ₇ O ₄ S
286426	OH	NH	CH	C ₂₈ H ₂₆ N ₆ O ₄ S

SOURCE – Boehringer Ingelheim.**REFERENCES**

- Hauel, N. et al. (Boehringer Ingelheim Pharma KG) *Disubstd. bicyclic heterocycles having, in particular, a thrombin inhibitive effect*. DE 19834751, WO 0008014.

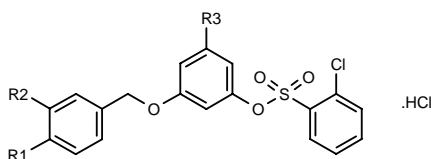
286676

2-Chlorobenzenesulfonic acid 3-(3-amidinobenzyloxy)-5-methylphenyl ester hydrochloride



C₂₁ H₁₉ Cl N₂ O₄ S . HCl; Mol wt: 467.3710

ACTION – A representative compound from a series of amidino and benzamidino derivatives that act as inhibitors of proteases, especially trypsin-like serine proteases such as chymotrypsin, trypsin, thrombin, plasmin and factor Xa. *In vitro*, compound was shown to inhibit factor Xa with a K_i value of 2.72 μ M. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
286677	H	C(=NH)NHOH	Me	C ₂₁ H ₁₉ ClN ₂ O ₅ S.HCl
286678	H	C(=NH)NHMe	Me	C ₂₂ H ₂₁ ClN ₂ O ₄ S.HCl
286679	C(=NH)NH ₂	H	Me	C ₂₁ H ₁₉ ClN ₂ O ₄ S.HCl
286680	H	C(=NH)NH ₂	H	C ₂₀ H ₁₇ ClN ₂ O ₄ S.HCl

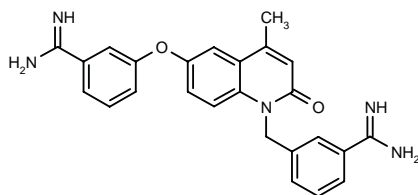
SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

1. Lu, T. et al. (3-Dimensional Pharmaceuticals, Inc.) *Amidino protease inhibitors*. JP 2000503010, US 6034127, WO 9724135.

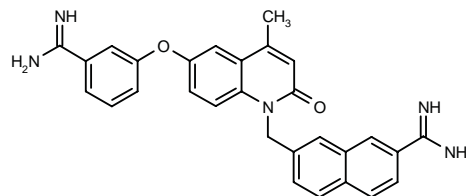
287085

3-[6-(3-Amidinophenoxy)-4-methyl-2-oxo-1,2-dihydroquinolin-1-ylmethyl]benzamidine



C₂₅ H₂₃ N₅ O₂; Mol wt: 425.4897

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of factor Xa. Another specifically claimed compound from this series of 2-oxo-2H-quinoline derivatives is:



287086: C₂₉ H₂₅ N₅ O₂

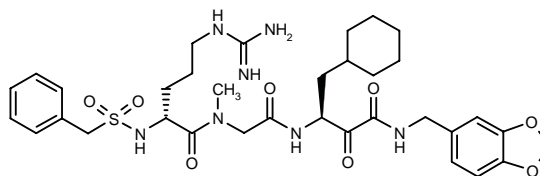
SOURCE – Merck KGaA.

REFERENCES

1. Gante, J. et al. (Merck Patent GmbH) *2-Oxo-2H-quinoline derivs*. DE 19839499, WO 0012479.

287368

N-(1,3-Benzodioxol-5-ylmethyl)-3(S)-[N²-(benzylsulfonyl)-L-arginyl-N²-methylglycinamido]-4-(cyclohexyl)-2-oxobutyramide



C₃₄ H₄₇ N₇ O₈ S; Mol wt: 713.8523

ACTION – Anticoagulant, a potent inhibitor of factor Xa (IC_{50} = 0.78 nM) with good selectivity relative to other serine proteases including thrombin, plasmin and human trypsin (IC_{50} > 1500 nM); it showed only modest activity against prothrombinase (IC_{50} = 9.0 nM).

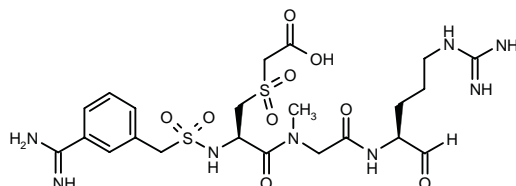
SOURCE – Corvas.

REFERENCES

1. Semple, J.E. et al. *Novel, potent, and selective factor Xa inhibitors featuring a hydrophobic P1-ketoamide moiety*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 193.

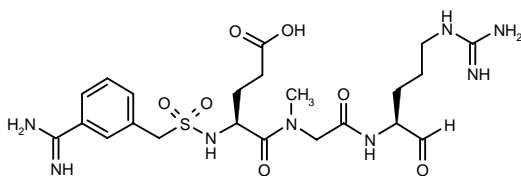
287503

N-[2(R)-(3-Amidinobenzylsulfonamido)-3-(carboxymethylsulfonyl)propionyl]-N-methylglycyl-L-arginal



C₂₂ H₃₄ N₈ O₉ S₂; Mol wt: 618.6896

ACTION – Anticoagulant, a potent transition-state factor Xa inhibitor (IC_{50} = 3.19 nM) with high selectivity over related serine proteases including plasmin, trypsin and thrombin (IC_{50} > 1500 nM). Another related compound is:



287504: C22 H34 N8 O7 S

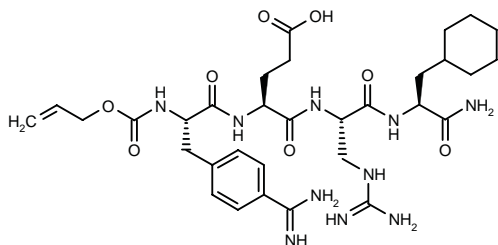
SOURCE – Corvas.

REFERENCES

1. Araldi, G.L. et al. *Synthesis and structure-activity relationships of novel transition-state factor Xa inhibitors featuring a bis-cationic system*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 191.

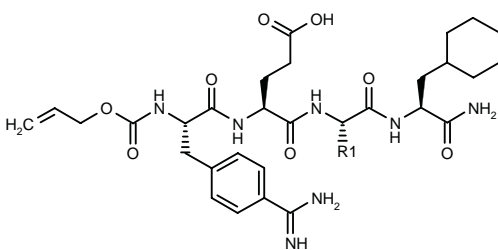
287612

N-Allyloxycarbonyl-L-(4-amidino)phenylalanyl-L-glutamyl-L-(2-amino-3-guanidinopropionyl)-L-cyclohexylalaninamide

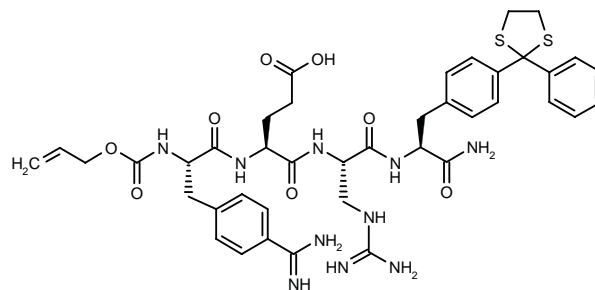


C32 H48 N10 O8; Mol wt: 700.7932

ACTION – Factor VIIa inhibitor giving a K_i value of 0.012 μ M for VIIa inhibition, while having no substantial inhibitory activity against factor Xa or other serine proteases such as thrombin. Potentially useful for the treatment and prophylaxis of thromboembolic diseases including thrombosis, restenosis, infarction and angina. Other exemplified compounds include the following:



Compound	R1	Formula
287613	CH ₂ CH ₂ NHC(=NH)NH ₂	C ₃₃ H ₅₀ N ₁₀ O ₈
287614	(CH ₂) ₃ NHC(=NH)NHNO ₂	C ₃₄ H ₅₁ N ₁₁ O ₁₀
287615	3-indolyl-CH ₂	C ₃₉ H ₅₀ N ₈ O ₈
287616	Ph	C ₃₆ H ₄₇ N ₇ O ₈
287618	(R)-CH(Me)OCH ₂ Ph	C ₃₈ H ₅₁ N ₇ O ₁₀



287617: C41 H50 N10 O8 S2

SOURCE – Aventis Pharma.

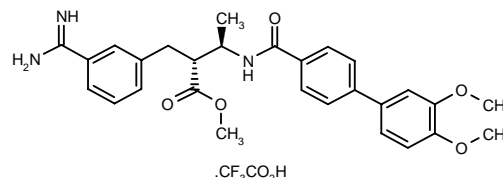
REFERENCES

1. Safar, P. et al. (Aventis Pharma Deutschland GmbH) *Factor VIIa inhibitors*. EP 0987274, WO 0015658.

RPR-208566

286957

2(*R*)-(3-Amidinobenzyl)-3(*R*)-(3',4'-dimethoxybiphenyl-4-ylcarboxamido)butyric acid methyl ester trifluoroacetate



C28 H31 N3 O5 . C2 H F3 O2; Mol wt: 603.5908

ACTION – Anticoagulant, a potent, reversible and direct factor Xa inhibitor ($K_i = 1.31$ nM) with high selectivity over plasmin, trypsin, thrombin, activated protein C and tissue plasminogen activator ($K_i = 890, 190, > 3950, > 18,400$ and > 8600 nM, respectively). In a rat model of carotid artery thrombosis, compound given by i.v. bolus at a dose of 500 μ g/kg followed by an infusion of 50 μ g/kg/min for 1 h prolonged the time to occlusion to 56 min and reduced thrombus mass from 7.3 (vehicle) to 3.0 mg. It produced no significant changes in activated thromboplastin time or prothrombin time, indicating that it does not significantly alter systemic coagulation.

SOURCE – Aventis Pharma.

REFERENCES

1. Klein, S.I. et al. (Aventis Pharmaceuticals, Inc.) *Substd. N-[(aminoiminomethyl or aminomethyl)phenyl]propyl amides*. CA 2264556, EP 0931060, WO 9900356.

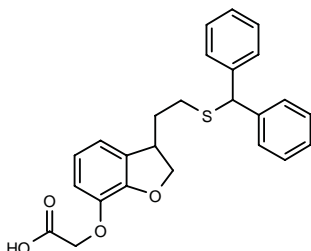
2. Heran, C. et al. *Antithrombotic efficacy of RPR208566 a factor Xa inhibitor in a rat model of carotid artery thrombosis*. FASEB J 1998, 12(5): A716.

3. Heran, C. et al. *Antithrombotic efficacy of RPR208566, a novel factor Xa inhibitor, in a rat model of carotid artery thrombosis*. Eur J Pharmacol 2000, 389(2-3): 201.

ANTIPLATELET THERAPY

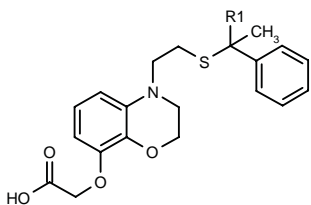
286590

2-[3-[2-(Diphenylmethylsulfanyl)ethyl]-2,3-dihydro-benzofuran-7-yloxy]acetic acid



C₂₅ H₂₄ O₄ S; Mol wt: 420.5266

ACTION – Potent Tx_A₂ and PGI₂ IP receptor antagonist, as demonstrated in binding assays by K_i values of 0.070 and 0.23 μM, respectively, for human Tx_A₂ and IP receptors. In addition, compound was shown to inhibit U-46619- and ADP-induced aggregation of human platelet-rich plasma (PRP) with IC₅₀ values of 0.55 and 0.95 μM, respectively. Other fused benzene heterocyclic compounds include the following:



Compound	R1	Formula
286591	Ph	C ₂₆ H ₂₇ NO ₄ S
286592	Me	C ₂₁ H ₂₅ NO ₄ S

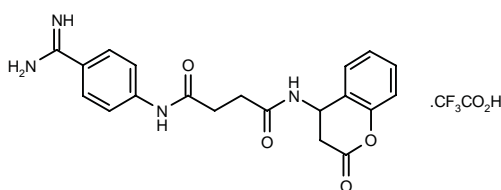
SOURCE – Toray.

REFERENCES

1. Ohtake, A. et al. (Toray Industries, Inc.) *Fused benzene heterocycle derivs. and utilization thereof*. WO 0007992.

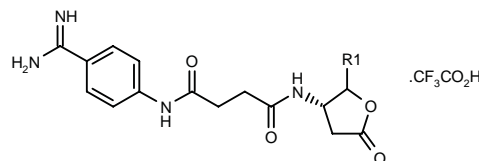
286978

N¹-(4-Amidinophenyl)-N⁴-(2-oxo-3,4-dihydro-2H-1-benzopyran-4-yl)succinamide trifluoroacetate



C₂₀ H₂₀ N₄ O₄ . C₂ H F₃ O₂; Mol wt: 494.4239

ACTION – Platelet aggregation inhibitor shown to inhibit ADP-induced aggregation of canine platelet-rich plasma *in vitro*, as well as collagen-induced platelet aggregation *ex vivo* in dogs. Other specifically claimed compounds from this series of substituted aminobenzamidinosuccinyl lactone derivatives include the following:



Compound	R1	Formula
286979	H	C ₁₅ H ₁₈ N ₄ O ₄ .C ₂ HF ₃ O ₂
286980	Ph	C ₂₁ H ₂₂ N ₄ O ₄ .C ₂ HF ₃ O ₂
286981	4-F-Ph	C ₂₁ H ₂₁ FN ₄ O ₄ .C ₂ HF ₃ O ₂
286982	2-thiazolyl	C ₁₈ H ₁₉ N ₅ O ₄ S.C ₂ HF ₃ O ₂
286983	vinyl	C ₁₇ H ₂₀ N ₄ O ₄ .C ₂ HF ₃ O ₂
286984	1,3-benzodioxol-5-yl	C ₂₂ H ₂₂ N ₄ O ₆ .C ₂ HF ₃ O ₂

SOURCE – Pharmacia.

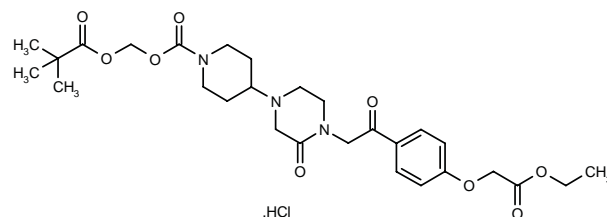
REFERENCES

1. Bovy, P.R. et al. (G.D. Searle & Co.) *Aminobenzamidinosuccinyl lactone derivs. useful as inhibitors of platelet aggregation*. US 6037365.

ME-3230*,2-5

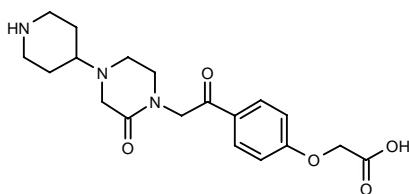
283483

4-[4-[2-[4-(Ethoxycarbonylmethoxy)phenyl]-2-oxoethyl]-3-oxopiperazin-1-yl]piperidine-1-carboxylic acid pivaloyloxymethyl ester hydrochloride



C₂₈ H₃₉ N₃ O₉ . HCl; Mol wt: 598.0890

ACTION – Oral antiplatelet agent, a double prodrug of the potent gpIIb/IIIa (fibrinogen) receptor antagonist **EF-5154** (IC₅₀ = 37 and 55 nM, respectively, against binding of fibrinogen and von Willebrand factor to gpIIb/IIIa, respectively) proven to inhibit human platelet aggregation induced by various agonists including ADP, collagen, U-46619 and epinephrine plus serotonin. The prodrug given orally at 1 mg/kg to dogs produced almost complete inhibition of *ex vivo* platelet aggregation at 1-2 h post-dosing, with approximately 50% inhibition remaining 8 h later; it was also effective in a sodium laurate-induced hind limb lesion model in guinea pigs. Compound had an oral bioavailability of > 40% in dogs, which was not affected by food, and it was shown to increase bleeding time to at most twice the baseline value at doses producing up to 90% inhibition of platelet aggregation.



EF-5154 [237370],1,3,4:** C₁₉ H₂₅ N₃ O₅

SOURCE – Meiji Seika.

REFERENCES

1. Katano, K. et al. (Meiji Seika Kaisha, Ltd.) *Novel cpd. having platelet aggregation inhibitor effect*. EP 0721941, US 5814636, WO 9602503.
2. Ota, K. et al. (Meiji Seika Kaisha, Ltd.) *Nitrogen-containing heterocyclic cpds. having antiplatelet aggregation effect and medicinal use thereof*. WO 9952894.
3. Kato, E. et al. *Pharmacological profiles of ME3230, a novel orally active GPIIb/IIIa antagonist*. Jpn J Pharmacol 2000, 82(Suppl. 1): Abst P-377.
4. Ohuchi, S. et al. *ME3230, an orally active GPIIb/IIIa antagonist*. Thromb Haemost 1999, (Suppl.): Abst 2706.
5. *Meiji Seika issues updated product pipeline*. DailyDrugNews.com (Daily Essentials) 1999, Oct 5.

*Identified compound **283483** (see **283482**) Drug Data Rep 2000, 022(01): 0039.

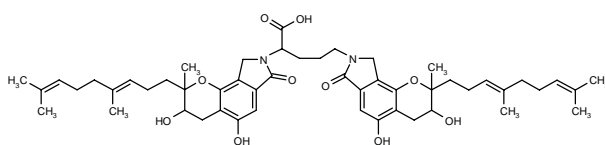
Identified compound **237370 (see **235110**) Drug Data Rep 1996, 018(07): 0620.

THROMBOLYTICS

SMTP-7

287124

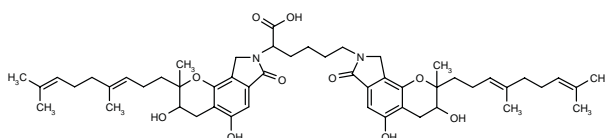
2,5-Bis[3,5-dihydroxy-2-methyl-2-[4,8-dimethyl-3(*E*),7-nonadienyl]-7-oxo-2,3,4,7,8,9-hexahydropyrano[2,3-*e*]-isoindol-8-yl]pentanoic acid



C₅₁ H₆₈ N₂ O₁₀; Mol wt: 869.1022

Light brown oil, $[\alpha]_D^{20}$ -35.87° (c 0.85, MeOH).

ACTION – Plasminogen activator, a staplabin analogue isolated from *Stachybotrys microspora* IFO 30018, proven to enhance severalfold urokinase-catalyzed plasminogen activation and plasminogen-fibrin binding, as well as urokinase- and plasminogen-mediated fibrinolysis, at concentrations of 80-150 μ M; it had no effect on plasminogen activation in the absence of urokinase. Another staplabin analogue is:



SMTP-8 [287125]: C₅₂ H₇₀ N₂ O₁₀

SOURCE – University of Tokyo, Tokyo (JP).

REFERENCES

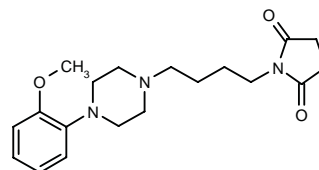
1. Hu, W. et al. *Activation of fibrinolysis by SMTP-7 and -8, novel staplabin analogs with a pseudosymmetric structure*. J Antibiot 2000, 53(3): 241.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

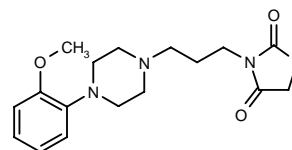
286720

1-[4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl]pyrrolidine-2,5-dione



C₁₉ H₂₇ N₃ O₃; Mol wt: 345.4403

ACTION – α_1 -Adrenoceptor antagonist with selectivity for α_{1A} -adrenoceptors over α_{1B} - and α_{1D} -adrenoceptors, as demonstrated in binding experiments by K_i values of 1 and 35 nM against [³H]-prazosin binding to α_{1A} - (rat submaxillary membrane) and α_{1B} -adrenoceptors (rat liver), respectively, and in functional studies by pK_B values of 9.0, 8.0 and 8.3, respectively, for inhibition of phenylephrine-induced contractions in rat prostate (α_{1A}) and spleen (α_{1B}) and norepinephrine-induced contractions in rat aorta (α_{1D}). The compound shows certain uroselectivity *in vivo*, as demonstrated by its greater ability to inhibit phenylephrine-induced increases in urethral pressure as compared to blood pressure in anesthetized dogs (pK_B = 7.9 and 7.4, respectively). Potentially useful for the treatment of benign prostatic hypertrophy. Other compounds from this series of arylpiperazine derivatives include the following:

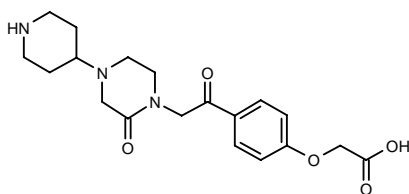


Compound	R1	Formula
286722	-CH ₂ -	C ₁₈ H ₂₅ N ₃ O ₃
286723	-(CH ₂) ₂ -	C ₁₉ H ₂₇ N ₃ O ₃

SOURCE – Ranbaxy.

REFERENCES

1. Anand, N. et al. (Ranbaxy Laboratories Ltd.) *Arylpiperazine derivs. useful as uroselective α_1 -adrenoceptor blockers*. WO 0005205.



EF-5154 [237370],1,3,4:** C₁₉ H₂₅ N₃ O₅

SOURCE – Meiji Seika.

REFERENCES

1. Katano, K. et al. (Meiji Seika Kaisha, Ltd.) *Novel cpd. having platelet aggregation inhibitor effect*. EP 0721941, US 5814636, WO 9602503.
2. Ota, K. et al. (Meiji Seika Kaisha, Ltd.) *Nitrogen-containing heterocyclic cpds. having antiplatelet aggregation effect and medicinal use thereof*. WO 9952894.
3. Kato, E. et al. *Pharmacological profiles of ME3230, a novel orally active GPIIb/IIIa antagonist*. Jpn J Pharmacol 2000, 82(Suppl. 1): Abst P-377.
4. Ohuchi, S. et al. *ME3230, an orally active GPIIb/IIIa antagonist*. Thromb Haemost 1999, (Suppl.): Abst 2706.
5. *Meiji Seika issues updated product pipeline*. DailyDrugNews.com (Daily Essentials) 1999, Oct 5.

*Identified compound **283483** (see **283482**) Drug Data Rep 2000, 022(01): 0039.

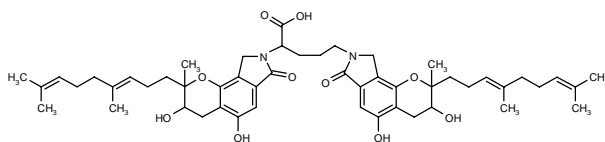
Identified compound **237370 (see **235110**) Drug Data Rep 1996, 018(07): 0620.

THROMBOLYTICS

SMTP-7

287124

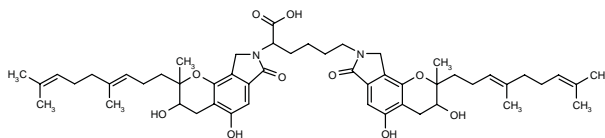
2,5-Bis[3,5-dihydroxy-2-methyl-2-[4,8-dimethyl-3(*E*),7-nonadienyl]-7-oxo-2,3,4,7,8,9-hexahydropyrano[2,3-*e*]-isoindol-8-yl]pentanoic acid



C₅₁ H₆₈ N₂ O₁₀; Mol wt: 869.1022

Light brown oil, $[\alpha]_D^{20}$ -35.87° (c 0.85, MeOH).

ACTION – Plasminogen activator, a staplabin analogue isolated from *Stachybotrys microspora* IFO 30018, proven to enhance severalfold urokinase-catalyzed plasminogen activation and plasminogen-fibrin binding, as well as urokinase- and plasminogen-mediated fibrinolysis, at concentrations of 80-150 μ M; it had no effect on plasminogen activation in the absence of urokinase. Another staplabin analogue is:



SMTP-8 [287125]: C₅₂ H₇₀ N₂ O₁₀

SOURCE – University of Tokyo, Tokyo (JP).

REFERENCES

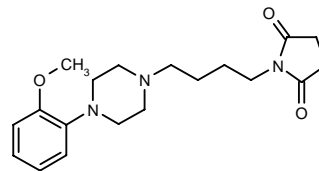
1. Hu, W. et al. *Activation of fibrinolysis by SMTP-7 and -8, novel staplabin analogs with a pseudosymmetric structure*. J Antibiot 2000, 53(3): 241.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

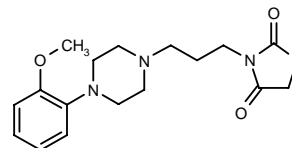
286720

1-[4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl]pyrrolidine-2,5-dione



C₁₉ H₂₇ N₃ O₃; Mol wt: 345.4403

ACTION – α_1 -Adrenoceptor antagonist with selectivity for α_{1A} -adrenoceptors over α_{1B} - and α_{1D} -adrenoceptors, as demonstrated in binding experiments by K_i values of 1 and 35 nM against [³H]-prazosin binding to α_{1A} - (rat submaxillary membrane) and α_{1B} -adrenoceptors (rat liver), respectively, and in functional studies by pK_B values of 9.0, 8.0 and 8.3, respectively, for inhibition of phenylephrine-induced contractions in rat prostate (α_{1A}) and spleen (α_{1B}) and norepinephrine-induced contractions in rat aorta (α_{1D}). The compound shows certain uroselectivity *in vivo*, as demonstrated by its greater ability to inhibit phenylephrine-induced increases in urethral pressure as compared to blood pressure in anesthetized dogs (pK_B = 7.9 and 7.4, respectively). Potentially useful for the treatment of benign prostatic hypertrophy. Other compounds from this series of arylpiperazine derivatives include the following:



Compound	R1	Formula
286722	-CH ₂ -	C ₁₈ H ₂₅ N ₃ O ₃
286723	-(CH ₂) ₂ -	C ₁₉ H ₂₇ N ₃ O ₃

SOURCE – Ranbaxy.

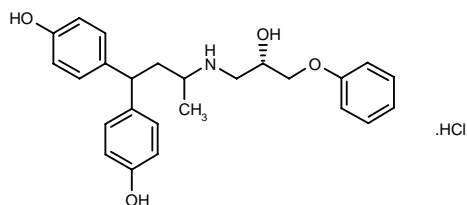
REFERENCES

1. Anand, N. et al. (Ranbaxy Laboratories Ltd.) *Arylpiperazine derivs. useful as uroselective α_1 -adrenoceptor blockers*. WO 0005205.

TREATMENT OF URINARY INCONTINENCE

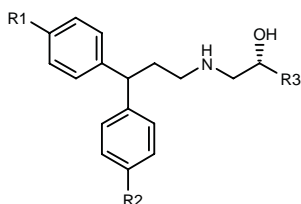
287178

1-[3,3-Bis(4-hydroxyphenyl)-1-methylpropylamino]-3-phenoxy-2(*S*)-propanol hydrochloride



C₂₅ H₂₉ N O₄ . HCl; Mol wt: 443.9680

ACTION – β_3 -Adrenoceptor agonist with potential in the treatment or prevention of urinary incontinence, pollakiuria, ulcers and pancreatitis, as well as for use as a lipolytic agent. *In vivo*, compound produced significant inhibition of the carbachol-induced increase in intravesical pressure in anesthetized dogs at a dose of 0.01 mg/kg i.v. Other compounds from this series of aminoalcohol derivatives include the following:



Compound	R1=R2	R3	Formula
287179	OMe	4-OH-3-(MeSO ₂ NH)-PhOCH ₂	C ₂₇ H ₃₄ N ₂ O ₇ S
287180	OMe	4-OH-3-(MeSO ₂ NH)-Ph	C ₂₆ H ₃₂ N ₂ O ₆ S
287181	NHCO ₂ Me	CH ₂ OPh	C ₂₈ H ₃₃ N ₃ O ₆

SOURCE – Fujisawa.

REFERENCES

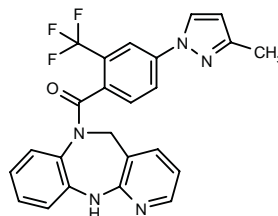
1. Taniguchi, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Aminoalcohol derivs. and their use as β_3 adrenergic agonists*. WO 0012462.

TREATMENT OF RENAL DISEASES

WAY-141608

287343

1-[6,11-Dihydro-6*H*-pyrido[2,3-*b*][1,5]benzodiazepin-6-yl]-1-[4-(3-methyl-1*H*-pyrazol-1-yl)-2-(trifluoromethyl)phenyl]-methanone



C₂₄ H₁₈ F₃ N₅ O; Mol wt: 449.4342

ACTION – Potent and selective, orally active, nonpeptide vasopressin V₂ receptor agonist with relatively weak binding affinity for cloned human V₂ receptors (IC₅₀ = 493 nM) and human V_{1A} receptors (IC₅₀ = 954 nM), and no affinity for human V_{1B} receptors. However, it exhibited full agonist activity in an *in vitro* functional assay using LV2 cells expressing human V₂ receptors (IC₅₀ = 1.7 nM) and lack of V_{1A} or oxytocin receptor-agonist activity, as demonstrated using rat tail arteries and uterine strips. *In vivo*, orally administered compound exhibited antidiuretic effects, producing a dose-dependent reduction in urine volume without altering urinary electrolyte excretion profile in both normal water-loaded rats and Brattleboro rats (ED₅₀ = 0.08 and < 0.1 mg/kg p.o., respectively), as well as in dogs and monkeys (ED₅₀ = 3 mg/kg p.o.). Potentially useful for the treatment of disease states associated with urine volume overflow such as diabetes insipidus, nocturnal enuresis, nocturia and some forms of urinary incontinence.

SOURCE – Wyeth-Ayerst.

REFERENCES

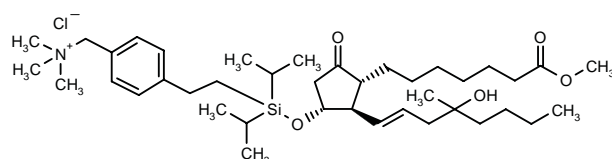
1. Failli, A.A. et al. (American Home Products Corp.) *Tricyclic vasopressin agonists*. EP 1000059, WO 9906403.
2. Sumsy, J.S. et al. *Pyridobenzodiazepines: Synthesis and structure-activity relationship of a novel class of orally active vasopressin V₂ receptor agonists*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 201.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

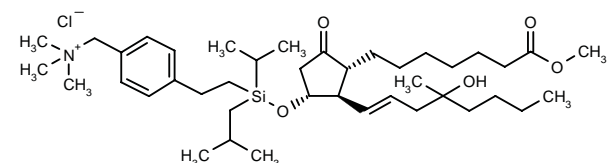
286548

[4-[2-[[[(1*R*,2*R*,3*R*)-2-[4-Hydroxy-4-methyl-1(*E*)-octenyl]-3-[6-(methoxycarbonyl)hexyl]-4-oxocyclopentyl]oxy][bis-(isopropyl)silyl]ethyl]phenyl]-*N,N,N*-trimethylmethanaminium chloride

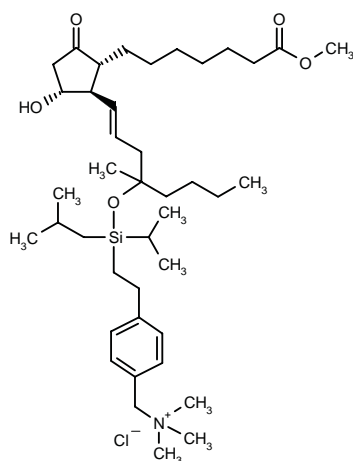


C40 H70 Cl N O5 Si ; Mol wt: 708.5340

ACTION – Silyl ether prodrug of the gastrointestinally active agent misoprostol designed to be hydrolyzed at low pH, enabling the release of the active drug in the gastric pH range. Potentially useful for the treatment or prevention of gastric ulcers. Other compounds from this series of gastrospecific prodrugs include the following:



286549: C41 H72 Cl N O5 Si



286550: C41 H72 N Cl O5 Si

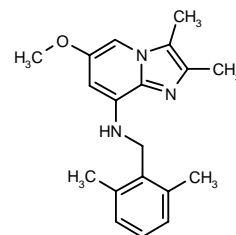
SOURCE – Pharmacia.

REFERENCES

1. Tremont, S.J. and Collins, P.W. (Monsanto Co.) *Gastro-specific prodrugs*. US 6030959.

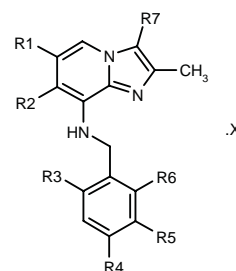
286796

N-(2,6-Dimethylbenzyl)-*N*-(6-methoxy-2,3-dimethylimidazo[1,2-*a*]pyridin-8-yl)amine



C19 H23 N3 O; Mol wt: 309.4107

ACTION – Agent for the treatment of gastrointestinal inflammatory diseases and gastric acid-related diseases such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome, an H⁺/K⁺-ATPase inhibitor. Other compounds from this series of substituted imidazo[1,2-*a*]pyridines include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	X	Formula
286797	H	H	Me	H	H	Me	Cl		C ₁₇ H ₁₈ ClN ₃
286798	H	H	OCF ₃	H	H	H	Me	HCl	C ₁₇ H ₁₆ F ₃ N ₃ O .HCl
286799	Me	H	Cl	H	H	Me	Me		C ₁₈ H ₂₀ ClN ₃
286800	H	H	H	H	OCHF ₂	H	Me	HCl	C ₁₇ H ₁₇ F ₂ N ₃ O .HCl
286801	Me	H	Me	F	H	Me	H		C ₁₈ H ₂₀ FN ₃
286802	H	H	OH	H	H	Me	Me		C ₁₇ H ₁₉ N ₃ O
286803	H	N(SO ₂ Me) ₂	Me	H	H	Me	Me		C ₂₀ H ₂₈ N ₄ O ₄ S ₂

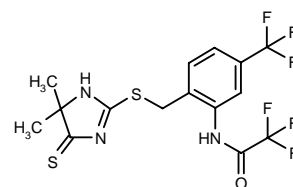
SOURCE – AstraZeneca.

REFERENCES

1. Amin, K. et al. (Astra AB) *New cpds*. WO 0011000.

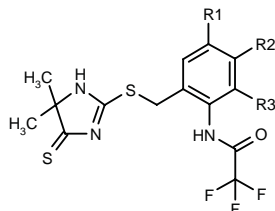
286906

N-[2-(5,5-Dimethyl-4-thioxo-4,5-dihydro-1*H*-imidazol-2-yl)sulfanylmethyl]-5-(trifluoromethyl)phenyl]-2,2,2-trifluoroacetamide



C15 H13 F6 N3 O S2; Mol wt: 429.4077

ACTION – Antiulcer agent and gastric secretion inhibitor shown to inhibit HCl/ethanol-induced ulcers in rats by 98.9% at a dose of 30 mg/kg p.o., as well as gastric acid secretion in pylorus-ligated rats by 80.1% at this dose. LD₅₀ > 4000 mg/kg p.o. in mice. A representative compound from a series of imidazoline derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
286908	F	Me	H	C ₁₅ H ₁₅ F ₄ N ₃ OS ₂
286909	H	F	Me	C ₁₅ H ₁₅ F ₄ N ₃ OS ₂
286910	Me	F	H	C ₁₅ H ₁₅ F ₄ N ₃ OS ₂

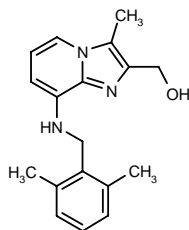
SOURCE – Arax.

REFERENCES

- Okabe, S. et al. (Arax Co., Ltd.) *Imidazoline derivs., their preparation method, and medicines*. JP 2000044542.

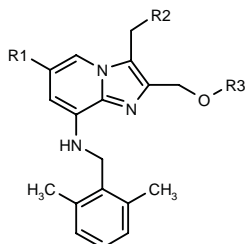
286936

[8-(2,6-Dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methanol



C₁₈H₂₁N₃O; Mol wt: 295.3839

ACTION – Agent for the treatment of gastrointestinal inflammatory diseases and gastric acid-related diseases such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome, an H⁺/K⁺-ATPase inhibitor. Other compounds from this series of substituted imidazo[1,2-a]pyridines include the following:



Compound	R1	R2	R3	Formula
286937	Me	H	H	C ₁₉ H ₂₃ N ₃ O
286938	H	H	CO ₂ Et	C ₂₁ H ₂₅ N ₃ O ₃
286939	H	H	COCH ₂ CO ₂ Et	C ₂₃ H ₂₇ N ₃ O ₄
286940	H	H	COCH ₂ CH ₂ CO ₂ H	C ₂₂ H ₂₅ N ₃ O ₄
286941	H	H	COCH ₂ N(Me) ₂	C ₂₂ H ₂₈ N ₄ O ₂
286942	H	OH	H	C ₁₈ H ₂₁ N ₃ O ₂

SOURCE – AstraZeneca.

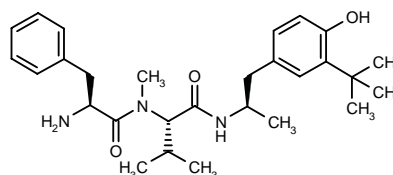
REFERENCES

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IRRITABLE BOWEL SYNDROME THERAPY

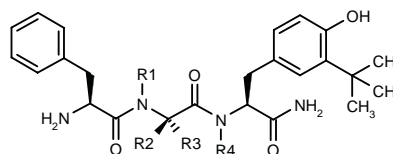
286913

L-Phenylalanyl-(N²-methyl)-L-valine N¹-[2-[3-(*tert*-butyl)-4-hydroxyphenyl]-1(*R*)-methylethyl]amide



C₂₈H₄₁N₃O₃; Mol wt: 467.6499

ACTION – Agent for the treatment of irritable bowel syndrome with motilin receptor-antagonist activity, as demonstrated in a binding assay by an IC₅₀ value of 1.9 nM against [¹²⁵I]-motilin binding in rabbit duodenal homogenates. Antagonist activity was demonstrated by its ability to inhibit acetylcholine-induced contractions of rabbit duodenal longitudinal muscle (pA₂ = 8.43). Other compounds from this series of phenethylamine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
286914	H	H	Ph	H	C ₃₀ H ₃₈ N ₄ O ₄
286915	Me	Ph	H	H	C ₃₁ H ₃₈ N ₄ O ₄
286916	Me	H	i-Pr	Me	C ₂₉ H ₄₂ N ₄ O ₄

SOURCE – Chugai.

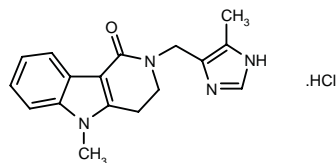
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- Kotake, K. et al. (Chugai Pharmaceutical Co. Ltd.) *Phenethyl amine derivs.* JP 2000044595.

ALOSETRON HYDROCHLORIDE

Rec INN; BAN; USAN

185981

5-Methyl-2-(5-methyl-1*H*-imidazol-4-ylmethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-1-one hydrochlorideGR-68755C⁺

C18 H19 N3 O . HCl; Mol wt: 329.8290

ACTION – Potent and selective 5-HT₃ receptor antagonist.

INDICATION – Treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea.

PRESENTATION – Tablets, 1.124 mg alosetron hydrochloride equiv. to 1 mg alosetron.

PROPRIETARY NAME – Lotronex (US).

SOURCE – Glaxo Wellcome.

RECENT REFERENCES

- Audolfsson, G. et al. *Effects of the 5-HT₃ receptor antagonist alosetron on neuromuscular transmission in canine and human intestinal muscle*. Aliment Pharmacol Ther 1999, 13(Suppl. 2): 39.
- Bush, T.G. et al. *Effects of alosetron on spontaneous migrating motor complexes in the isolated small and large intestine of the mouse*. Gastroenterology 2000, 118(4, Suppl. 2, Part 1): A401.
- Camilleri, M. et al. *Efficacy and safety of alosetron in women with irritable bowel syndrome: A randomised, placebo-controlled trial*. Lancet 2000, 355(9209): 1035.
- Camilleri, M. et al. *Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT₃ receptor antagonist*. Aliment Pharmacol Ther 1999, 13(9): 1149.
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- Gupta, S.K. et al. *Effect of alosetron (a new 5-HT₃ receptor antagonist) on the pharmacokinetics of haloperidol in schizophrenic patients*. J Clin Pharmacol 1995, 35(2): 202.
- Heath, M.R. et al. *Alosetron does not improve anxiety in female IBS patients*. Gastroenterology 2000, 118(4, Suppl. 2, Part 1): A616.
- Hedayetullah, N.S. et al. *Effect of alosetron on pharmacokinetics (PK) of theophylline*. Annu Meet Am Assoc Pharm Sci (Nov 14-18, New Orleans) 1999, Abst 2483.
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15. Lacey, L.A. et al. *Impact of alosetron on health related quality of life (HRQOL) and productivity in female patients with irritable bowel syndrome (IBS)*. Gut 1999, 45(Suppl. 5): Abst 61.03.

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22. Naliboff, B.D. et al. *Evidence for selective effect of the 5HT₃ antagonist alosetron on amygdala and hippocampal activation in IBS patients*. Gastroenterology 2000, 118(4, Suppl. 2, Part 1): A81.

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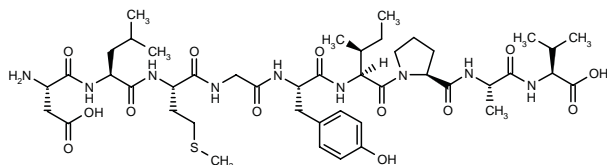
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*Drug Data Rep 1992, 014(01): 0017.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

286764

L-Aspartyl-L-leucyl-L-methionyl-glycyl-L-tyrosyl-L-isoleucyl-L-prolyl-L-alanyl-L-valine



C45 H71 N9 O13 S; Mol wt: 978.1719

ACTION – Immunogenic peptide derived from a hepatitis C virus (HCV) core protein that exhibits enhanced HLA-A2 binding affinity and cytotoxic T-lymphocyte recognition *in vitro* and enhanced immunogenicity *in vivo*, with potential in the treatment or prevention of HCV infection.

SOURCE – Department of Health & Human Services (US).

REFERENCES

- Berzofsky, J.A. et al. (Department of Health & Human Services) *Modified HCV peptide vaccines*. WO 0011186.

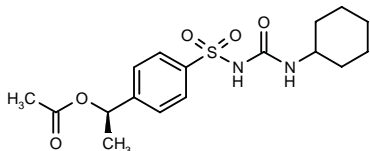
ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

(R)-ACX

282972

(+)-N-[4-[1(R)-Acetoxyethyl]phenylsulfonyl]-N'-cyclohexyleurea



C17 H24 N2 O5 S; Mol wt: 368.4516

ACTION – Hypoglycemic agent proven to strongly stimulate the release of insulin from cultured pancreatic β -cells established from SV-40-transformed hamster islet cells. *In vivo*, compound showed a rapid-onset and short-lasting hypoglycemic effect compared to acetohexamide and glibenclamide when administered orally to fasted rats, and it was shown to suppress the increase in blood glucose levels due to starch loading in fasted mice; its rapid onset and short duration of action are thought to result from rapid absorption and elimination of both

compound and its metabolite. Potentially useful particularly in the control of postprandial hyperglycemia in patients with type 2 diabetes.

SOURCE – Godo Shusei.

REFERENCES

- Akita, H. et al. (Godo Shusei Co., Ltd.) *Sulfonylurea derivs. and drugs containing the same*. JP 1999335347, WO 9948864.
- Akita, H. et al. *Determination of absolute configuration of a metabolite (-)-hydroxyhexamide from acetohexamide, syntheses of (-)-and (+)-hydroxyhexamides and (-)-and (+)-acetohexamides*. Tetrahedron Asymmetry 1998, 9: 4331.
- Akita, H. et al. *Enzymatic synthesis of (-)-and (+)-acetohexamides and (-)- and (+)-hydroxyhexamides*. Chem Pharm Bull 1999, 47(8): 1164.
- Akita, H. et al. *Synthesis of enantiomerically pure both sulfonyl urea compounds characterized by short lasting hypoglycemic effect*. 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 1P-06.
- Seri, K. et al. *(R)-ACX is a novel sulfonylurea compound with potent, quick and short-lasting hypoglycemic activity*. Eur J Pharmacol 2000, 389(2-3): 253.

286751

L-Lysyl-L-cysteinyl-L-asparaginyl-L-threonyl-L-alanyl-L-threonyl-L-cysteinyl-L-alanyl-L-threonyl-L-alanyl-L-arginyl-L-leucyl-L-alanyl-L-alanyl-L-phenylalanyl-L-leucyl-L-alanyl-L-arginyl-L-seryl-L-seryl-glycyl-L-tyrosinamide cyclic (S-3.2-S-3.7)-disulfide

C96 H157 N31 O29 S2; Mol wt: 2273.6160

ACTION – Peptide with calcitonin- and amylin-agonist activity, potentially useful for the treatment of diabetes, including type 1 and type 2 diabetes, as well as for regulating gastrointestinal motility. Compound is reported to exhibit advantages over amylin by virtue of its smaller size and molecular weight, which makes it easier and more economical to synthesize, as well as more amenable to drug delivery via patch, microsphere and/or buccal technology. Agonist activity was determined *in vitro* by measuring its ability to bind to amylin receptors in rat brain preparations using [125 I]-rat amylin as the ligand ($IC_{50} = 1.9$ nM), as well as to calcitonin C1a receptors in transfected HEK293 cells using [125 I]-human calcitonin as the ligand ($IC_{50} = 0.093$ nM). *In vivo*, it was equipotent to rat amylin in inhibiting phenol red gastric emptying in rats. Other exemplified peptides include the following:

L-Cysteinyl-L-asparaginyl-L-threonyl-L-alanyl-L-threonyl-L-cysteinyl-L-alanyl-L-threonyl-L-alanyl-L-arginyl-L-leucyl-L-alanyl-L-alanyl-L-phenylalanyl-L-leucyl-L-alanyl-L-arginyl-L-serinamide cyclic (S-3.1-S-3.6)-disulfide

286752: C76 H128 N26 O23 S2

L-Lysyl-L-cysteinyl-L-asparaginyl-L-threonyl-L-alanyl-L-threonyl-L-cysteinyl-L-alanyl-L-threonyl-L-alanyl-L-arginyl-L-leucyl-L-alanyl-L-asparaginyl-L-phenylalanyl-L-leucyl-L-valyl-L-arginyl-L-seryl-L-seryl-glycyl-L-tyrosinamide cyclic (S-3.2-S-3.7)-disulfide

286754: C99 H162 N32 O30 S2

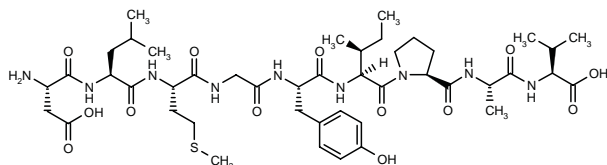
L-Leucyl-L-seryl-L-threonyl-L-alanyl-L-alanyl-L-threonyl-L-alanyl-L-arginyl-L-leucyl-L-alanyl-L-alanyl-L-phenylalanyl-L-leucyl-L-alanyl-L-arginyl-serinamide

286755: C71 H123 N23 O20

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

286764

L-Aspartyl-L-leucyl-L-methionyl-glycyl-L-tyrosyl-L-isoleucyl-L-prolyl-L-alanyl-L-valine



C45 H71 N9 O13 S; Mol wt: 978.1719

ACTION – Immunogenic peptide derived from a hepatitis C virus (HCV) core protein that exhibits enhanced HLA-A2 binding affinity and cytotoxic T-lymphocyte recognition *in vitro* and enhanced immunogenicity *in vivo*, with potential in the treatment or prevention of HCV infection.

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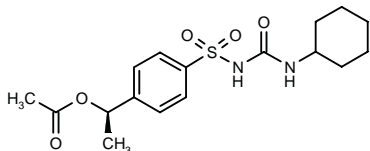
ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

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282972

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4. Akita, H. et al. *Synthesis of enantiomerically pure both sulfonyl urea compounds characterized by short lasting hypoglycemic effect*. 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 1P-06.
5. Seri, K. et al. *(R)-ACX is a novel sulfonylurea compound with potent, quick and short-lasting hypoglycemic activity*. Eur J Pharmacol 2000, 389(2-3): 253.

286751

L-Lysyl-L-cysteinyl-L-asparaginyl-L-threonyl-L-alanyl-L-threonyl-L-cysteinyl-L-alanyl-L-threonyl-L-alanyl-L-arginyl-L-leucyl-L-alanyl-L-alanyl-L-phenylalanyl-L-leucyl-L-alanyl-L-arginyl-L-seryl-L-seryl-glycyl-L-tyrosinamide cyclic (S-3.2-S-3.7)-disulfide

C96 H157 N31 O29 S2; Mol wt: 2273.6160

ACTION – Peptide with calcitonin- and amylin-agonist activity, potentially useful for the treatment of diabetes, including type 1 and type 2 diabetes, as well as for regulating gastrointestinal motility. Compound is reported to exhibit advantages over amylin by virtue of its smaller size and molecular weight, which makes it easier and more economical to synthesize, as well as more amenable to drug delivery via patch, microsphere and/or buccal technology. Agonist activity was determined *in vitro* by measuring its ability to bind to amylin receptors in rat brain preparations using [125 I]-rat amylin as the ligand ($IC_{50} = 1.9$ nM), as well as to calcitonin C1a receptors in transfected HEK293 cells using [125 I]-human calcitonin as the ligand ($IC_{50} = 0.093$ nM). *In vivo*, it was equipotent to rat amylin in inhibiting phenol red gastric emptying in rats. Other exemplified peptides include the following:

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286752: C76 H128 N26 O23 S2

L-Lysyl-L-cysteinyl-L-asparaginyl-L-threonyl-L-alanyl-L-threonyl-L-cysteinyl-L-alanyl-L-threonyl-L-alanyl-L-arginyl-L-leucyl-L-alanyl-L-asparaginyl-L-phenylalanyl-L-leucyl-L-valyl-L-arginyl-L-seryl-L-seryl-glycyl-L-tyrosinamide cyclic (S-3.2-S-3.7)-disulfide

286754: C99 H162 N32 O30 S2

L-Leucyl-L-seryl-L-threonyl-L-alanyl-L-alanyl-L-threonyl-L-alanyl-L-arginyl-L-leucyl-L-alanyl-L-alanyl-L-phenylalanyl-L-leucyl-L-alanyl-L-arginyl-serinamide

286755: C71 H123 N23 O20

L-Cysteiny-L-asparaginy-L-threony-L-alanyl-L-threony-L-cysteiny-L-alanyl-L-threony-L-glutaminy-L-arginy-L-leucyl-L-alanyl-L-asparaginy-L-phenylalanyl-L-leucyl-L-valyl-L-arginy-L-seryl-L-seryl-glycyl-L-tyrosinamide cyclic (S-3.1-S-3.6)-disulfide

286756: C95 H153 N31 O30 S2

L-Lysyl-L-cysteiny-L-asparaginy-L-threony-L-alanyl-L-threony-L-cysteiny-L-alanyl-L-threony-L-glutaminy-L-arginy-L-leucyl-L-alanyl-L-asparaginy-L-phenylalanyl-L-leucyl-L-valyl-L-arginy-L-seryl-L-seryl-glycyl-L-tyrosinamide cyclic (S-3.2-S-3.7)-disulfide

286757: C101 H165 N33 O31 S2

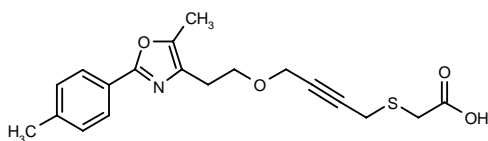
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REFERENCES

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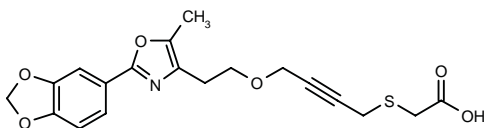
287074

2-[4-[2-[5-Methyl-2-(4-methylphenyl)oxazol-4-yl]ethoxy]-2-butylnylsulfanyl]acetic acid



C19 H21 N O4 S; Mol wt: 359.4439

ACTION – Peroxisome proliferator-activated receptor (PPAR) modulator that is reported to act preferably on PPAR α and PPAR γ subtypes, potentially useful in the treatment or prevention of diabetes, obesity, metabolic disorders, hyperlipidemia, arteriosclerosis, hypertension, circulatory diseases and ischemic heart disease. Compound was shown to significantly reduce blood glucose and triglyceride levels in KKA γ mice when given in the diet at a dose of 44.7 mg/kg/day, and it also significantly reduced plasma total cholesterol and triglycerides and nonsignificantly reduced free fatty acids in cholesterol-fed rats given a single dose of 20 mg/kg p.o. Another compound from this series of carboxylic acid derivatives is:



287075: C19 H19 N O6 S

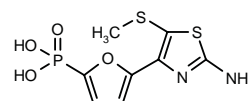
SOURCE – Ono.

REFERENCES

1. Tajima, H. et al. (Ono Pharmaceutical Co., Ltd.) *Carboxylic acid derivs. and drugs containing the same as the active ingredient*. WO 0012491.

287240

5-[2-Amino-5-(methylsulfanyl)thiazol-4-yl]furan-2-yl-phosphonic acid



C8 H9 N2 O4 P S2; Mol wt: 292.2751

ACTION – Agent for the treatment of type 2 diabetes, an inhibitor of fructose-1,6-bisphosphatase (FBPase; IC₅₀ = 0.015 and 0.25 μ M, respectively, against human and rat liver enzyme). In addition, compound was shown to inhibit gluconeogenesis in rat hepatocytes (IC₅₀ = 10 μ M). When tested *in vivo* in fasted rats, it was shown to reduce glucose levels following i.v. (52 and 73% decrease, respectively, at 3 and 10 mg/kg) and p.o. administration (70% decrease at 30 mg/kg). Compound was also effective in decreasing glucose levels in Zucker diabetic fatty rats following i.v. infusion (29 and 39% decrease, respectively, at 3 and 30 mg/kg/h x 6 h) and p.o. administration (15.4% decrease at 100 mg/kg p.o.) and was found to inhibit gluconeogenesis in these animals (75% inhibition at 3 mg/kg/h i.v. x 6 h). In addition, administration of 100 mg/kg p.o. of compound resulted in the normalization of hepatic glycogen levels in *db/db* mice. Compound is estimated to have an oral bioavailability in rats of about 18%. A representative compound from a series of heteroaromatic compounds bearing a phosphonate moiety.

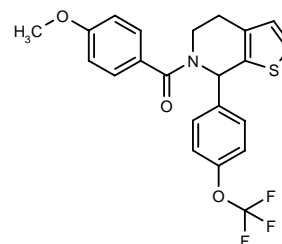
SOURCE – Metabasis.

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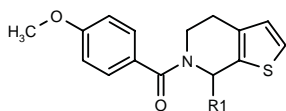
287261

1-(4-Methoxyphenyl)-1-[7-[4-(trifluoromethoxy)phenyl]-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-6-yl]methanone



C22 H18 F3 N O3 S; Mol wt: 433.4482

ACTION – Glucose-6-phosphatase inhibitor with potential in the treatment of disorders of the endocrinological system, particularly hyperglycemia and diabetes, especially non-insulin-dependent diabetes mellitus (NIDDM). Other exemplified compounds from this series of 4,5,6,7-tetrahydrothieno[2,3-c]pyridine derivatives include the following:



Compound	R1	Formula
287262	4-Cl-Ph	C ₂₁ H ₁₈ ClNO ₂ S
287264	4-MeO-Ph	C ₂₂ H ₂₁ NO ₃ S
287265	4-MeO-cyclohexyl	C ₂₂ H ₂₇ NO ₃ S
287266	1-Me-4-Pip	C ₂₁ H ₂₆ N ₂ O ₂ S
287267	3-THF	C ₁₉ H ₂₁ NO ₃ S

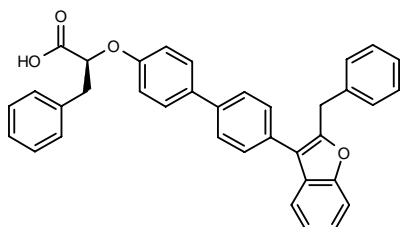
SOURCE – Novo Nordisk.

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1. Madsen, P. et al. (Novo Nordisk A/S) *4,5,6,7-Tetrahydro-thieno[2,3-c]pyridine derivs.* WO 0014090.

287486

2(S)-[4'-(2-Benzyl-1-benzofuran-3-yl)biphenyl-4-yloxy]-3-phenylpropionic acid



C36 H28 O4; Mol wt: 524.6132

M.p. 167-9 °C; [α]_D²⁵ -13.4° (*c* 1.0, THF).

ACTION – Antidiabetic agent, an inhibitor of human protein-tyrosine-phosphatase PTP1B (IC₅₀ = 0.32 μM) with 10-100-fold selectivity over other PTPs including LAR, PTPα, VH-R and He-PTP (IC₅₀ = 3.25, 33.7, 15.9 and 7.1 μM, respectively). In diabetic *ob/ob* mice, compound was shown to normalize plasma glucose levels at doses of 25 mg/kg p.o. and 1 mg/kg i.p.

SOURCE – Wyeth-Ayerst.

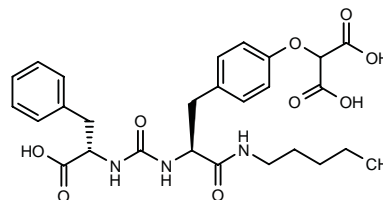
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1. Malamas, M.S. et al. (American Home Products Corp.) *Biphenyl oxo-acetic acids useful in the treatment of insulin resistance and hyperglycemia.* WO 9958518.
2. Malamas, M.S. et al. *Novel benzofuran and benzothiophene biphenyls as inhibitors of protein tyrosine phosphatase 1B with antihyperglycemic properties.* J Med Chem 2000, 43(7): 1293.

PNU-177496

286887

2-[4-[2(S)-[3-[1(S)-Carboxy-2-phenylethyl]ureido]-2-(N-pentylcarbamoyl)ethyl]phenoxy]malonic acid



C27 H33 N3 O9; Mol wt: 543.5697

ACTION – Protein-tyrosine-phosphatase PTP1B inhibitor (K_i = 3.4 μM) potentially useful as an insulin-sensitizing agent for the treatment of type 2 diabetes.

SOURCE – Pharmacia.

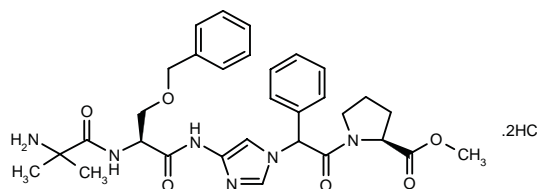
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1. Larsen, S.D. et al. (Pharmacia & Upjohn Co.) *Inhibitors of protein tyrosine phosphatase.* WO 9911606.
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TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

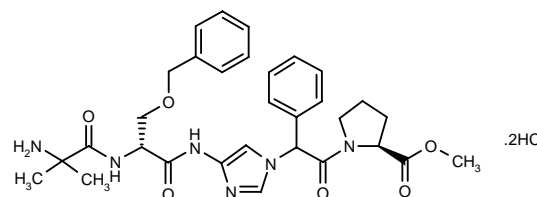
286760

1-[2-[4-[2(S)-(2-Amino-2-methylpropionamido)-3-(benzyloxy)propionamido]-1H-imidazol-1-yl]-2-phenylacetyl]pyrrolidine-2(S)-carboxylic acid dihydrochloride



C31 H38 N6 O6 . 2HCl; Mol wt: 663.5990

ACTION – Growth hormone (GH) secretagogue proven to enhance GH secretion in rat pituitary cell cultures with an EC₅₀ of 2.39 mM. Another exemplified compound is:



286761: C31 H38 N6 O6 . 2HCl

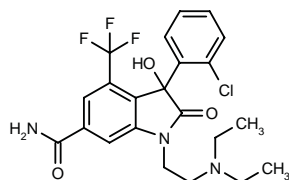
SOURCE – Lilly.

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1. Dodge, J.A. et al. (Eli Lilly and Company) *Growth hormone secretagogues.* WO 0010565.

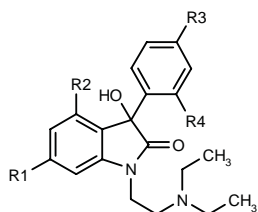
286920

3-(2-Chlorophenyl)-1-[2-(diethylamino)ethyl]-3-hydroxy-2-oxo-4-(trifluoromethyl)-2,3-dihydro-1*H*-indole-6-carboxamide



C₂₂ H₂₃ Cl F₃ N₃ O₃; Mol wt: 469.8887

ACTION – Growth hormone (GH) secretagogue that was shown to stimulate GH release from rat pituitary cells *in vitro* with an EC₅₀ of 0.5 nM and to significantly increase the weight of rats treated at a dose of 10 mg/kg/day p.o. b.i.d. x 9 days. Other exemplified compounds from this series of oxindole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
286921	H	Br	H	F	C ₂₀ H ₂₂ BrFN ₂ O ₂
286922	4-morpholinyl- -COCH ₂ CH ₂ -ethynylene	CF ₃	H	Cl	C ₃₀ H ₃₃ ClF ₃ N ₃ O ₄
286923	CONH ₂	CF ₃	Cl	Cl	C ₂₂ H ₂₂ Cl ₂ F ₃ N ₃ O ₃

SOURCE – Sumitomo Pharmaceuticals.

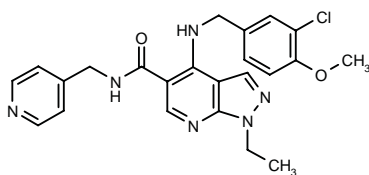
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1. Tokunaga, T. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Oxindole derivs. as growth hormone releasers*. WO 0010975.

TREATMENT OF MALE SEXUAL DYSFUNCTION

287567

4-(3-Chloro-4-methoxybenzylamino)-1-ethyl-*N*-(4-pyridinylmethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide



C₂₃ H₂₃ Cl N₆ O₂; Mol wt: 450.9277

ACTION – Potent and selective inhibitor of cGMP phosphodiesterase type 5 (PDE5), with potential in the treatment of erectile dysfunction and various cardiovascular disorders, a specifically claimed compound from a series of fused pyridine derivatives.

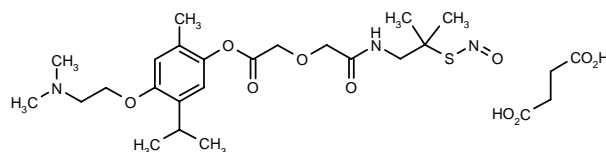
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Macor, J.E. and Yu, G. (Bristol-Myers Squibb Co.) *Fused pyridine inhibitors of cGMP phosphodiesterase*. WO 0015222.

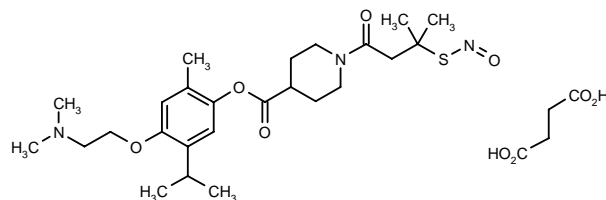
NMI-678-11**287347**

2-[2-[2-Methyl-2-(nitrososulfanyl)propylamino]-2-oxoethoxy]acetic acid 4-[2-(dimethylamino)ethoxy]-5-isopropyl-2-methylphenyl ester succinate



C₂₂ H₃₅ N₃ O₆ S . C₄ H₆ O₄; Mol wt: 587.6869

ACTION – α -Adrenoceptor antagonist with nitric oxide (NO) donor activity, proven to relax human corpus cavernosum strips and to increase intracavernosal pressure in rabbits. Potentially useful for the treatment of erectile dysfunction. Another specifically claimed compound within this series of nitrosylated moxislyte derivatives is:



NMI-937-11 [287373]: C₂₅ H₃₉ N₃ O₅ S . C₄ H₆ O₄

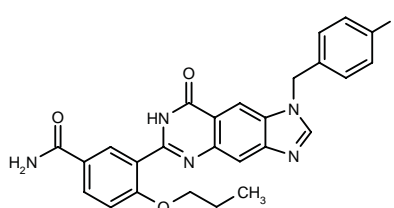
SOURCE – NitroMed.

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1. Garvey, D.S. et al. (NitroMed Inc.) *Nitrosated and nitrosylated α -adrenergic receptor antagonists, compsns. and methods of use*. WO 0012075.
2. Earl, R.A. et al. *Nitrosylated α -adrenergic receptor antagonists as potential agents for the treatment of erectile dysfunction*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 239.

287483

3-[1-(4-Fluorobenzyl)-8-oxo-7,8-dihydro-1*H*-imidazo-[4,5-*g*]quinazolin-6-yl]-4-propoxybenzamide



C₂₆ H₂₂ F N₅ O₃; Mol wt: 471.4898

Hydrochloride, light tan solid, m.p. 204-6 °C.

ACTION – Potent and selective phosphodiesterase type 5 (PDE5) inhibitor ($IC_{50} = 0.48$ nM) with improved potency and selectivity compared to sildenafil. In an *in vitro* functional assay, compound showed concentration-related activity (140% at 30 nM and 190% at 300 nM) in relaxing rabbit corpus cavernosum tissues. Potentially useful for the treatment of male erectile dysfunction.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Macor, J.E. et al. (Bristol-Myers Squibb Co.) *Quinazolinone inhibitors of cGMP phosphodiesterase*. WO 9964004.
2. Rotella, D.P. et al. *N-3-Substituted imidazoquinazolinones: Potent and selective PDE5 inhibitors as potential agents for treatment of erectile dysfunction*. J Med Chem 2000, 43(7): 1257.

CONTRACEPTIVES

287663

Human chorionic gonadotropin (hCG) vaccine containing the β -subunit of hCG joined to β -galactosidase and a chitosan-based adjuvant

ACTION – Female contraceptive vaccine comprising the β -subunit of human chorionic gonadotropin (β -hCG) fused to β -galactosidase and a chitosan-based adjuvant, preferably in an injectable formulation. The preferred amount of the β -hCG protein is about 250 μ g and the ratio of β -hCG to adjuvant is in the range 1/20 to 1/1500 (w/w). The vaccine stimulates the production of antibodies to endogenous β -hCG and induces transient infertility.

SOURCE – Zonagen.

REFERENCES

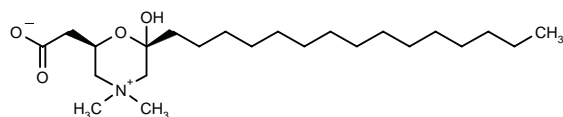
1. Harris, J. and Martinez, M. (Zonagen, Inc.) *Human chorionic gonadotropin vaccines*. WO 0015253.

Z-15

280665

2-[6(*S*)-Hydroxy-4,4-dimethyl-6-pentadecylmorpholinium-2(*R*)-yl]acetate

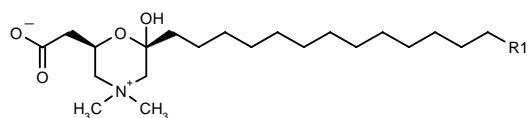
(+)-Hemipalmitoylcarnitinium



C23 H45 N O4; Mol wt: 399.6115

ACTION – Topical microbicial spermicide (minimum effective concentration [MEC] = 0.109 mg/ml) with antifungal activity against *Candida albicans* (MIC = 2 μ g/ml) and antiviral activity against HIV; its mechanism of action may involve its surfactant activity. When formulated in car-boxymethylcellulose, compound showed almost no irritation in the rabbit vaginal irritation test. Currently under-going evaluation in animal models for activity

against herpesvirus and *Haemophilus ducreyi*, a cofactor in HIV transmission. Potentially useful for protection against sexually transmitted diseases and pregnancy. Within this series of acylcarnitine analogues, the following are also described:



Compound	R1	Formula
Z-14 [287039]	Me	C ₂₂ H ₄₃ NO ₄
Z-13 [287040]	H	C ₂₁ H ₄₁ NO ₄

SOURCE – Virginia Tech, Blacksburg, VA (US).

REFERENCES

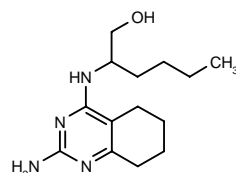
1. Savle, P.S. et al. *Acylcarnitine analogues as topical, microbicial spermicides*. Bioorg Med Chem Lett 1999, 9(17): 2545.
2. Savle, P.S. et al. *Multigram synthesis of enantiopure acylcarnitium analog Z-15 as a microbicial and spermicidal agent*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MED1 127.

DERMATOLOGIC DRUGS

TREATMENT FOR ALLERGIC SKIN DISORDERS

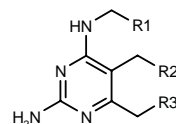
287103

2-(2-Amino-5,6,7,8-tetrahydroquinazolin-4-ylamino)-hexan-1-ol



C14 H24 N4 O; Mol wt: 264.3706

ACTION – Inhibitor of the production of Th2-type cytokines such as IL-4 and IL-5, proven to inhibit IL-4 production in murine lymph node cells with an IC_{50} of 0.1 μ g/ml and expected to be useful in the treatment of allergic diseases, autoimmune diseases such as systemic lupus erythematosus, AIDS, etc. Other exemplified pyrimidine derivatives include the following:



Compound	R1	R2	R3	Formula
287104	CH(OH)Pr	-(CH2)2-		C ₁₃ H ₂₂ N ₄ O
287105	Bu	Pr	H	C ₁₄ H ₂₆ N ₄
287106	Bu	-(CH2)2-		C ₁₃ H ₂₂ N ₄
287107	CH(OH)Pr	Pr	H	C ₁₄ H ₂₆ N ₄ O

ACTION – Potent and selective phosphodiesterase type 5 (PDE5) inhibitor ($IC_{50} = 0.48$ nM) with improved potency and selectivity compared to sildenafil. In an *in vitro* functional assay, compound showed concentration-related activity (140% at 30 nM and 190% at 300 nM) in relaxing rabbit corpus cavernosum tissues. Potentially useful for the treatment of male erectile dysfunction.

SOURCE – Bristol-Myers Squibb.

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CONTRACEPTIVES

287663

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SOURCE – Zonagen.

REFERENCES

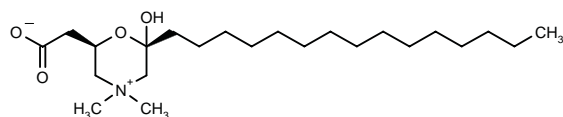
1. Harris, J. and Martinez, M. (Zonagen, Inc.) *Human chorionic gonadotropin vaccines*. WO 0015253.

Z-15

280665

2-[6(*S*)-Hydroxy-4,4-dimethyl-6-pentadecylmorpholinium-2(*R*)-yl]acetate

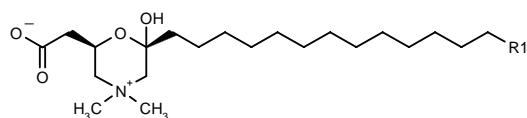
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C23 H45 N O4; Mol wt: 399.6115

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against herpesvirus and *Haemophilus ducreyi*, a cofactor in HIV transmission. Potentially useful for protection against sexually transmitted diseases and pregnancy. Within this series of acylcarnitine analogues, the following are also described:



Compound	R1	Formula
Z-14 [287039]	Me	C ₂₂ H ₄₃ NO ₄
Z-13 [287040]	H	C ₂₁ H ₄₁ NO ₄

SOURCE – Virginia Tech, Blacksburg, VA (US).

REFERENCES

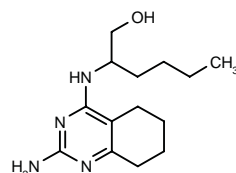
1. Savle, P.S. et al. *Acylcarnitine analogues as topical, microbicial spermicides*. Bioorg Med Chem Lett 1999, 9(17): 2545.
2. Savle, P.S. et al. *Multigram synthesis of enantiopure acylcarnitium analog Z-15 as a microbicial and spermicidal agent*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MED1 127.

DERMATOLOGIC DRUGS

TREATMENT FOR ALLERGIC SKIN DISORDERS

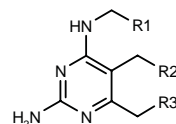
287103

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Compound	R1	R2	R3	Formula
287104	CH(OH)Pr	-(CH2)2-		C ₁₃ H ₂₂ N ₄ O
287105	Bu	Pr	H	C ₁₄ H ₂₆ N ₄
287106	Bu	-(CH2)2-		C ₁₃ H ₂₂ N ₄
287107	CH(OH)Pr	Pr	H	C ₁₄ H ₂₆ N ₄ O

SOURCE – Sumitomo Pharmaceuticals.

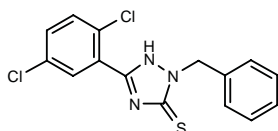
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ANTIPSORIATICS

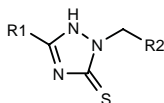
287052

2-Benzyl-5-(2,5-dichlorophenyl)-2,3-dihydro-1*H*-1,2,4-triazole-3-thione



C15 H11 Cl2 N3 S; Mol wt: 336.2449

ACTION – Chemokine, especially CXCR2, receptor modulator, with potential in the treatment of inflammatory disorders, particularly psoriasis. Other specifically claimed compounds from this series of 1,2,4-triazole-3-thione derivatives include the following:



Compound	R1	R2	Formula
287053	2-furyl	Ph	C ₁₃ H ₁₁ N ₃ OS
287054	2-Me-Ph	Ph	C ₁₆ H ₁₅ N ₃ S
287055	3-(PhO)-Ph	Ph	C ₂₁ H ₁₇ N ₃ OS
287056	1-Naph	Ph	C ₁₉ H ₁₅ N ₃ S
287057	2-Cl-Ph	4-CF ₃ -Ph	C ₁₆ H ₁₁ ClF ₃ N ₃ S
287058	2-Cl-Ph	3-Cl-PhCH ₂	C ₁₆ H ₁₃ Cl ₂ N ₃ S

SOURCE – AstraZeneca.

REFERENCES

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HU1124

236376

Humanized anti-CD11a monoclonal antibody that prevents T-cells from attacking other cells or tissues

ACTION – Recombinant humanized monoclonal antibody that targets the CD11a receptor on the surface of T-cells, which plays a major role in T-cell activation and migration. Compound is undergoing phase I/II clinical trials for the treatment of renal transplant rejection and has entered phase III for the treatment of psoriasis in subjects with moderate to severe plaque psoriasis. In phase II psoriasis studies, compound was shown to induce clinical and histological improvement and to inhibit the inflammatory

process as result of decreased T-cell activation, T-cell migration into skin and T-cell cytokine production.

SOURCES – Genentech; Xoma.

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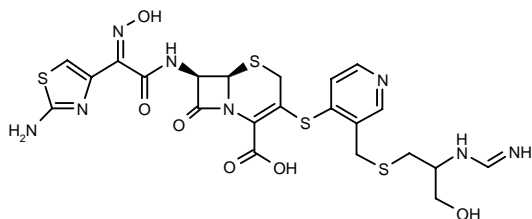
1. Bauer, R.J. et al. *Population pharmacokinetics and pharmacodynamics of the anti-CD11a antibody hu1124 in human subjects with psoriasis.* J Pharmacokinetic Biopharm 1999, 27(4): 397.
2. Garovoy, M.R. *An engineered human antibody to adhesion receptors (hu1124) in the treatment of psoriasis.* IBC Conf Psoriasis: Latest Adv Underst Nov Ther Approaches (May 12-13, London) 1997, 1997.
3. Gottlieb, A.B. et al. *Psoriasis is clinically and histologically improved by treatment with a humanized anti-CD11a monoclonal antibody (hu1124): Results of a multicenter, multiple ascending dose study.* Arthritis Rheum 1999, 42(9, Suppl.): Abst 1813.
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8. *Genentech and Xoma agree to develop jointly anti-CD11a for psoriasis and organ transplant rejection; GNE to buy 1.5 million shares of Xoma stock as part of agreement in which Xoma will develop anti-CD11a through phase II.* Genentech, Inc. Press Release 1996, April 22.
9. *hu1124 shows clinical activity in phase I for psoriasis.* DailyDrugNews.com (Daily Essentials) 1998, April 30.
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12. *Xoma and Genentech expand hu1124 collaboration to include transplantation.* DailyDrugNews.com (Daily Essentials) 1999, Aug 23.
13. *Xoma and Genentech extend hu1124 agreement; present preliminary results from psoriasis trial.* DailyDrugNews.com (Daily Essentials) 1999, April 20.
14. *Xoma completes phase II development of hu1124; Genentech will decide future course.* DailyDrugNews.com (Daily Essentials) 1999, Jan 11.
15. *Xoma completes phase II enrollment in psoriasis study.* DailyDrugNews.com (Daily Essentials) 1998, Oct 13.
16. *Xoma files IND to test hu1124 - anti-CD11a - in kidney transplant patients.* Xoma Corp. Press Release 1997, Jan 21.
17. *Xoma files IND to test hu1124 - anti-CD11a - in psoriasis.* Xoma Corp. Press Release 1996, Sept 5.
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22. *Xoma: Q4 and year-end 1997 highlights.* DailyDrugNews.com (Daily Essentials) 1998, March 6.
23. Xoma Corp. Press Release 1996, April 25.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

286547

(6*R*,7*R*)-7-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(hydroxyimino)-acetamido]-3-[3-[3-hydroxy-2-(iminomethylamino)-propylsulfanylmethyl]-4-pyridinylsulfanyl]-3-cephem-4-carboxylic acid



C₂₂ H₂₄ N₈ O₆ S₄; Mol wt: 624.7456

ACTION – Cephalosporin antibiotic active against a broad spectrum of microorganisms including organisms resistant to β -lactam antibiotics. *In vitro*, compound exhibited MIC values of 0.13, 1, 2, 0.25 and 8 μ g/ml, respectively, when tested against *Staphylococcus aureus* ATCC 29213, methicillin-resistant *S. aureus* ATCC 33593, methicillin-resistant *Staphylococcus haemolyticus* 05, vancomycin-resistant *Enterococcus faecalis* VanB and *Escherichia coli* ATCC 25992. *In vivo*, compound gave an ED₅₀ of 0.39 mg/kg s.c. in mice with lethal bacteremic peritonitis caused by a methicillin-susceptible strain of *S. aureus*, compared to values of 1.94 mg/kg and 0.06 mg/kg, respectively, for vancomycin and imipenem.

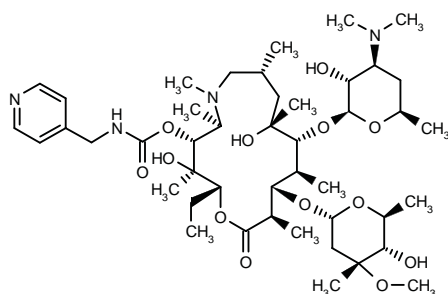
SOURCE – Microcide.

REFERENCES

1. Cho, I.-S. et al. (Microcide Pharmaceuticals, Inc.) *Cephalosporin antibiotics*. US 6030965.

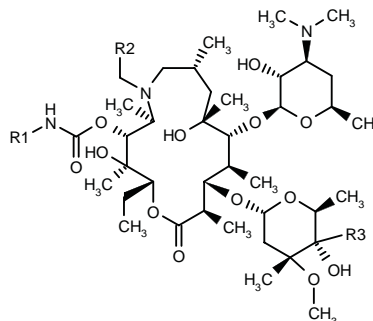
286724

9a-Aza-9-deoxo-9a-methyl-11-O-[*N*-(4-pyridylmethyl)-carbamoyl]-9a-homoerythromycin A



C₄₅ H₇₈ N₄ O₁₃; Mol wt: 883.1262

ACTION – Antibacterial and antiprotozoal agent, a representative compound from a series of C11 carbamate azalide derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
286725	3-Pyr-CH ₂ NH	H	H	C ₄₅ H ₇₉ N ₅ O ₁₃
286726	3-Pyr-CH ₂	H	4-Pyr-CH ₂ NHCH ₂	C ₅₂ H ₈₆ N ₆ O ₁₃
286727	2-Pyr-CH ₂	Me	H	C ₄₆ H ₈₀ N ₄ O ₁₃
286728	3-Pyr-CH ₂	vinyl	H	C ₄₇ H ₈₀ N ₄ O ₁₃

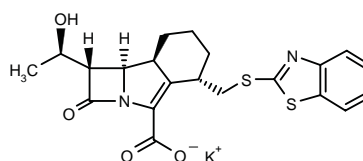
SOURCE – Pfizer.

REFERENCES

1. Cheng, H. et al. (Pfizer Products Inc.) *C11 carbamates of macrolide antibacterials*. EP 0984019, JP 2000063397, US 6043227.

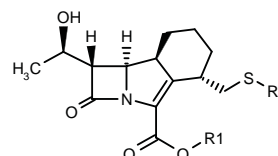
286847

(1*S*,5*S*,8*aS*,8*bR*)-5-(Benzothiazol-2-ylsulfanylmethyl)-1-[1(*R*)-hydroxyethyl]-2-oxo-1,2,5,6,7,8,8*a*,8*b*-octa-hydroazeto[2,1-*a*]isoindole-4-carboxylic acid potassium salt



C₂₁ H₂₁ K N₂ O₄ S₂; Mol wt: 468.6369

ACTION – Carbapenem antibiotic with potent *in vitro* activity against *Staphylococcus aureus* 209P (MIC = 0.01 μ g/ml or less), *S. aureus* 56R (MIC = 0.02 μ g/ml) and methicillin-resistant *S. aureus* 535 (MIC = 1.5 μ g/ml). Other exemplified compounds from this series of tricyclic carbapenems include the following:



Compound	R1	R2	Formula
286848	Na	CSN(Et)Ph	C ₂₃ H ₂₇ N ₂ NaO ₄ S ₂
286849	K	6-(4-Pyr-CONH)-2-benzothiazolyl	C ₂₇ H ₂₅ KN ₄ O ₅ S ₂

SOURCE – Sankyo.

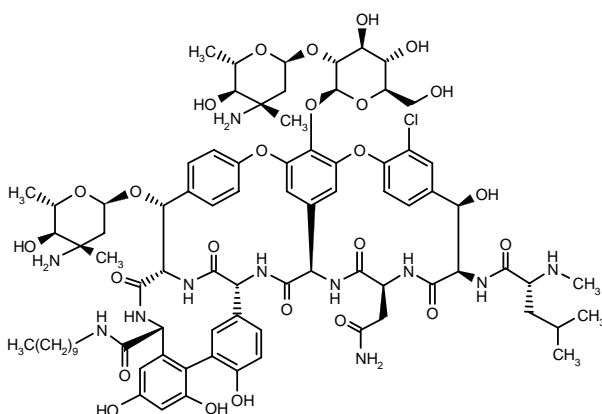
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1. Kawamoto, I. et al. (Sankyo Co., Ltd.) *Tricyclic carbapenem cpds.* JP 2000038387.

287132

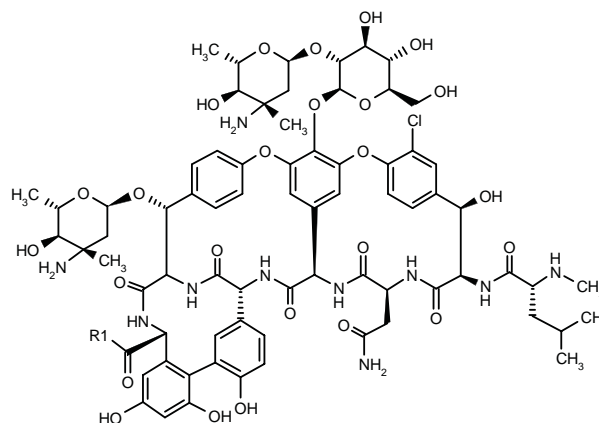
(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38*aR*)-22-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-L-arabinohexopyranosyloxy)-44-[2-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-L-arabinohexopyranosyl)-β-D-glucopyranosyloxy]-3-(carbamoylmethyl)-10-chloro-*N*-decyl-7,28,30,32-tetrahydroxy-6-(*N*²-methylleucylamido)-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38*a*-tetradecahydro-1*H*,22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-26-carboxamide

(4''*R*)-22-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-arabino-hexopyranosyl)-26-decarboxy-19-dechloro-26-(*N*-decylcarbamoyl)vancomycin



C83 H110 Cl N11 O25; Mol wt: 1697.2870

ACTION – Semisynthetic glycopeptide antibiotic, an eremomycin⁺ derivative proven active against highly resistant clinical strains, especially against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (MIC = 0.5, 1 and 1-2 μg/ml, respectively). Compound was significantly more active than teicoplanin and eremomycin against vancomycin-resistant *E. faecium* and was nearly as active as teicoplanin but more active than eremomycin against vancomycin-resistant *E. faecalis*. Other representative compounds within this series of eremomycin carboxamides are:



Compound	R1	Formula
287133	(S)-N(CH ₂) ₄ -CH(NH ₂)CONHC ₁₀ H ₂₁	C ₈₉ H ₁₂₂ ClN ₁₃ O ₂₆
287135	4-(C ₁₀ H ₂₁)-1-Piz	C ₈₇ H ₁₁₇ ClN ₁₂ O ₂₅
287136	4-Ph-PhCH ₂ N(Me)	C ₈₇ H ₁₀₂ ClN ₁₁ O ₂₅

SOURCES – Abbott; Institute of New Antibiotics, Moscow (RU).

REFERENCES

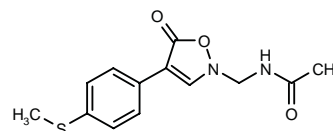
1. Miroshnikova, O.V. et al. *Structure-activity relationship in the series of eremomycin carboxamides.* J Antibiot 2000, 53(3): 286.

*Drug Data Rep 1988, 010(11): 0927.

ANTIBACTERIAL DRUGS

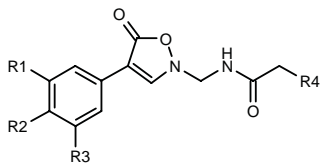
286805

N-[4-[4-(Methylsulfonyl)phenyl]-5-oxo-2,5-dihydro-isoxazol-2-ylmethyl]acetamide



C13 H14 N2 O3 S; Mol wt: 278.3306

ACTION – Antibacterial agent useful against infections caused by Gram-positive bacteria such as multiply resistant staphylococci, streptococci and enterococci including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. A representative compound from a series of isoxazolinone derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
286806	H	2-thienyl	H	H	C ₁₆ H ₁₄ N ₂ O ₃ S
286807	H	NH ₂	H	H	C ₁₂ H ₁₃ N ₃ O ₃
286808	F	OMe	H	H	C ₁₃ H ₁₃ FN ₂ O ₄
286809	F	OMe	H	Me	C ₁₄ H ₁₅ FN ₂ O ₄
286810	H	Br	H	H	C ₁₂ H ₁₁ BrN ₂ O ₃
286811	H	4-(4-F-PhOCO)-1-Piz	H	H	C ₂₃ H ₂₃ FN ₄ O ₅
286812	F	4-thiomorpholinyl	F	H	C ₁₆ H ₁₇ F ₂ N ₃ O ₃ S
286813	H	1,1-dioxo-4-thiomorpholinyl	H	H	C ₁₆ H ₁₉ N ₃ O ₅ S
286814	F	4-(COCH ₂ OH)-1-Piz	H	H	C ₁₈ H ₂₁ FN ₄ O ₅

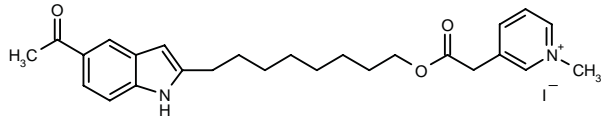
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Snyder, L.B. and Zheng, Z. (Bristol-Myers Squibb Co.) *Novel isoxazolinone antibacterial agents*. WO 0010566.

286816

3-[2-[8-(5-Acetyl-1*H*-indol-2-yl)octyloxy]-2-oxoethyl]-1-methylpyridinium iodide



C26 H33 I N2 O3; Mol wt: 548.4577

ACTION – Antibacterial agent that acts by selectively inhibiting bacterial nicotinamide adenine dinucleotide (NAD) synthetase (IC₅₀ = 25 μM), the enzyme catalyzing the final step in the biosynthesis of NAD. Compound exhibited a minimum toxic dose against human myeloid K562 cells of 500 μM.

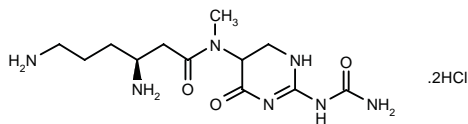
SOURCE – UAB Research Foundation, Birmingham, AL (US).

REFERENCES

1. Brouillette, W.J. et al. (UAB Research Foundation) *Inhibitors of bacterial NAD synthetase*. WO 0010996.

286958

3(*S*),6-Diamino-*N*-methyl-*N*-(4-oxo-2-ureido-1,4,5,6-tetrahydropyrimidin-5-yl)hexanamide dihydrochloride



C12 H23 N7 O3 . 2HCl; Mol wt: 386.2815

ACTION – Antibacterial agent, a derivative of the natural product TAN-1057⁺ with improved activity against resistant strains and reduced toxicity. *In vitro*, compound exhibited an MIC value of 0.2 μg/ml against *Staphylococcus aureus* 133 strain with intermediate resistance to TAN-1057-A,B, as compared to a value of 0.8 μg/ml for TAN-1057-A,B. *In vivo*, it exhibited comparable potency to TAN-1057-A,B when tested in *S. aureus* 133-infected mice, both compounds providing 100% survival at a dose of 1 mg/kg i.v. Compound exhibited much weaker acute toxicity than parent compound in mice following i.p. administration (LD₅₀ > 400 mg/kg vs. 100 mg/kg for TAN-1057-A,B), as well as weaker hepatic toxicity *in vitro* when tested in HepG2 cells.

SOURCE – Bayer.

REFERENCES

1. Brands, M. et al. (Bayer AG) *TAN-1057 derivs*. DE 19838998, WO 0012484.

*Drug Data Rep 1990, 012(11): 0929.

KASSINATUERIN-1

287620

Glycyl-L-phenylalanyl-L-methionyl-L-lysyl-L-tyrosyl-L-isoleucyl-glycyl-L-prolyl-L-leucyl-L-isoleucyl-L-prolyl-L-histidyl-L-alanyl-L-valyl-L-lysyl-L-alanyl-L-isoleucyl-L-seryl-L-aspartyl-L-leucyl-L-isoleucinamide

C109 H176 N26 O25 S; Mol wt: 2282.8130

ACTION – Antibacterial agent isolated from the skin of the frog *Kassina senegalensis*, with broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria and fungi including *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* (MIC = 8, 4 and 70 μM, respectively).

SOURCE – Creighton University, Omaha, NE (US).

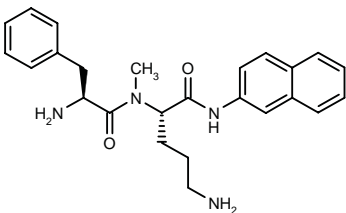
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1. Mattute, B. et al. *Kassinatuerin-1: A peptide with broad-spectrum antimicrobial activity isolated from the skin of the hyperoliid frog, Kassina senegalensis*. Biochem Biophys Res Commun 2000, 268(2): 433.

MC-002434*

283442

L-Phenylalanyl-*N*²-methyl-L-ornithine (2-naphthyl)amide



C25 H30 N4 O2; Mol wt: 418.5380

ACTION – Broad-spectrum *Pseudomonas aeruginosa* efflux pump inhibitor with minimal intrinsic antibacterial activity (MIC = 256 µg/ml) but able to strongly potentiate (8-fold at 5 µg/ml) the antibacterial activity of levofloxacin against *P. aeruginosa* PAM1032 overexpressing multi-drug-resistant efflux pumps. *In vivo*, combination with compound (30 mg/kg i.p.) was able to potentiate the activity of levofloxacin (30 mg/kg s.c.) in *P. aeruginosa* PAM1032-infected mice.

SOURCES – Daiichi Pharmaceutical; Microcide.

REFERENCES

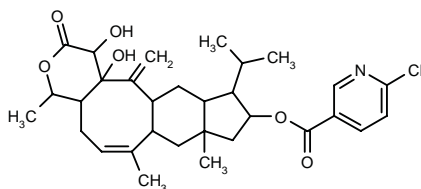
1. Chamberland, S. et al. (Microcide Pharmaceuticals, Inc.) *Efflux pump inhibitors*. WO 9937667.
2. Renau, T.E. et al. *Efflux pump inhibitors potentiate the antibacterial activity of levofloxacin in Pseudomonas aeruginosa*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 4.
3. Renau, T.E. et al. *Inhibitors of efflux pumps in Pseudomonas aeruginosa potentiate the activity of fluoroquinolone antibacterial levofloxacin*. J Med Chem 1999, 42(24): 4928.
4. Renau, T.E. et al. *Inhibitors of efflux pumps in Pseudomonas aeruginosa potentiate the activity of the fluoroquinolone antibacterial levofloxacin*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F1265.

*Identified compound **283442** Drug Data Rep 2000, 022(03): 0260.

ANTIFUNGAL AGENTS

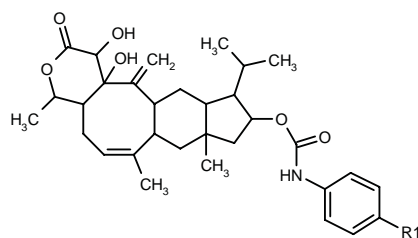
286595

6-Chloropyridine-3-carboxylic acid 1,13a-dihydroxy-11-isopropyl-4,7,8a-trimethyl-13-methylene-2-oxo-1,2,4,4a,5,7a,8,8a,9,10,11,11a,12,12a,13,13a-hexadecahydroindeno[5',6':4,5]cycloocta[1,2-c]pyran-10-yl ester



C31 H40 Cl N O6; Mol wt: 558.1110

ACTION – Antifungal agent, a derivative of the natural product BE-49385A with more potent *in vitro* activity against *Trichosporon cutaneum* IFO 1189 (MIC = 3.13 µg/ml vs. 100 µg/ml or greater for BE-49385A and amphotericin B). Other related compounds include the following:



Compound	R1	Formula
286597	F	C ₃₂ H ₄₂ FN ₆ O ₆
286598	H	C ₃₂ H ₄₃ N ₆ O ₆

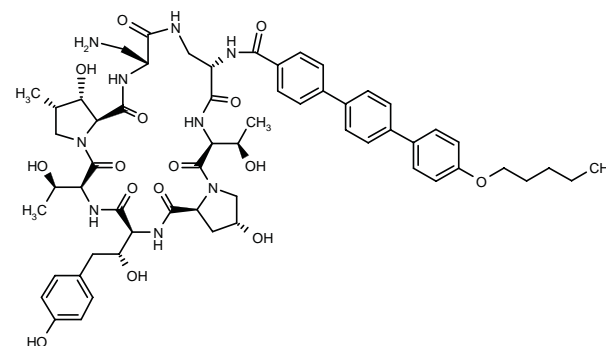
SOURCE – Banyu.

REFERENCES

1. Hirano, A. et al. (Banyu Pharmaceutical Co., Ltd.) *Sesterterpene derivs. exhibiting antifungal activities*. WO 0008010.

286753

(2*R*,6*S*,9*S*,13*R*,15*aS*,16*S*,17*S*,21*S*,24*S*,26*aS*)-13-(Aminomethyl)-2,16-dihydroxy-6,21-bis[1(*R*)-hydroxyethyl]-24-[1(*R*)-hydroxy-2-(4-hydroxyphenyl)ethyl]-17-methyl-9-[4-[4'-(pentyloxy)biphenyl-4-yl]benzamido]-perhydro-1*H*,5*H*-dipyrrolo[1,2-*d*:1,2-*m*]-[1,4,7,10,13,16,19]heptaazacyclodocosine-5,8,12,15,20,23,26-heptaone



C59 H75 N9 O15; Mol wt: 1150.2900

ACTION – Antifungal and antiparasitic agent with MIC values of 0.078, 0.625, 5.0, > 20 and 0.312 µg/ml against *Candida albicans*, *Candida parapsilosis*, *Aspergillus fumigatus*, *Cryptococcus neoformans* and *Histoplasma capsulatum*, respectively. A representative compound from a series of ring-modified cyclic peptide analogues of echinocandins.

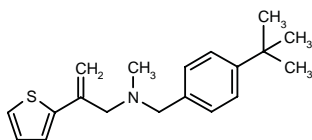
SOURCE – Lilly.

REFERENCES

1. Borromeo, P.S. et al. (Eli Lilly and Company) *Ring modified cyclic peptide analogs*. WO 0011023.

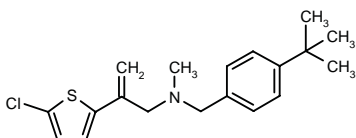
286834

N-(4-*tert*-Butylbenzyl)-*N*-methyl-*N*-[2-(2-thienyl)-2-propenyl]amine



C19 H25 N S; Mol wt: 299.4795

ACTION – Antifungal agent with potent activity against *Trichophyton mentagrophytes* TIMM1189 (MIC = 0.4 µg/ml). Another exemplified compound is:



286836: C19 H24 Cl N S

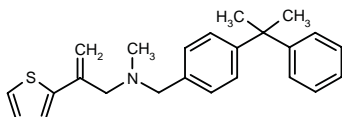
SOURCE – Pola Chemical.

REFERENCES

1. Yuasa, M. et al. (Pola Chemical Industries Inc.) *Anti-fungal agents*. JP 2000034287.

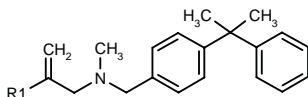
286837

N-Methyl-*N*-[4-(1-methyl-1-phenylethyl)benzyl]-*N*-[2-(2-thienyl)-2-propenyl]amine



C24 H27 N S; Mol wt: 361.5503

ACTION – Antifungal agent with potent activity against *Trichophyton mentagrophytes* TIMM1189 (MIC = 0.03 µg/ml). Other exemplified compounds include the following:



Compound	R1	Formula
286838	2,4-(Me)2-5-thiazolyl	C ₂₅ H ₃₀ N ₂ S
286839	2,5-(Cl)2-3-thienyl	C ₂₄ H ₂₅ Cl ₂ NS
286840	3-thienyl	C ₂₄ H ₂₇ NS

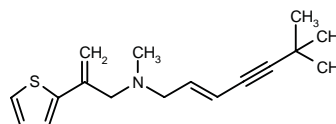
SOURCE – Pola Chemical.

REFERENCES

1. Yuasa, M. et al. (Pola Chemical Industries Inc.) *Anti-fungal agents*. JP 2000034285.

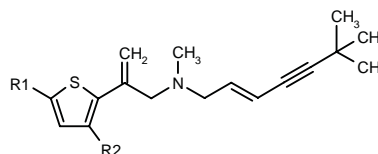
286841

N-[6,6-Dimethylhept-2(*E*)-en-4-ynyl]-*N*-methyl-*N*-[2-(2-thienyl)-2-propenyl]amine



C17 H23 N S; Mol wt: 273.4417

ACTION – Antifungal agent with potent activity against *Trichophyton mentagrophytes* TIMM1189 (MIC = 0.05 µg/ml). Other exemplified compounds include the following:



Compound	R1	R2	Formula
286842	H	Cl	C ₁₇ H ₂₂ ClNS
286843	Cl	H	C ₁₇ H ₂₂ ClNS

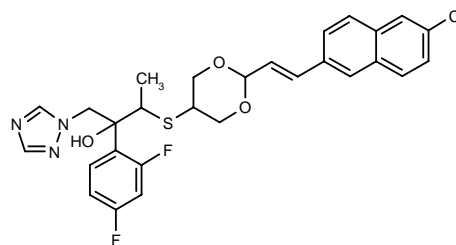
SOURCE – Pola Chemical.

REFERENCES

1. Yuasa, M. et al. (Pola Chemical Industries Inc.) *Anti-fungal agents containing sulfur*. JP 2000034230.

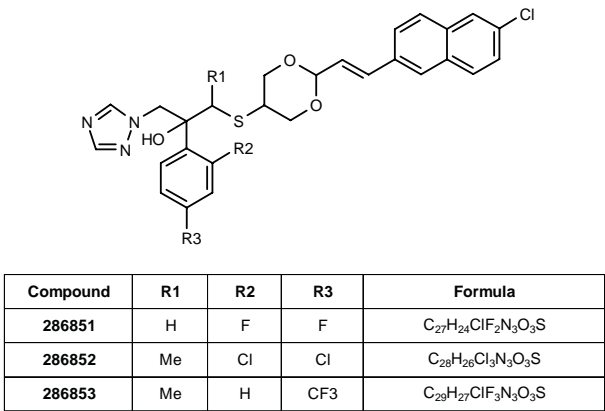
286850

3-[2-[(*E*)-2-(6-Chloronaphthalen-2-yl)vinyl]-1,3-dioxan-5-ylsulfanyl]-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol



C28 H26 Cl F2 N3 O3 S; Mol wt: 558.0464

ACTION – Triazole antifungal agent proven active in a murine model of systemic candidiasis, providing 100% survival on day 21 postinoculation when given at a dose of 20 mg/kg p.o. at 1, 4 and 24 h after inoculum, compared to 60% survival for animals treated with fluconazole at the same dose. Other exemplified compounds include the following:



SOURCE – Sankyo.

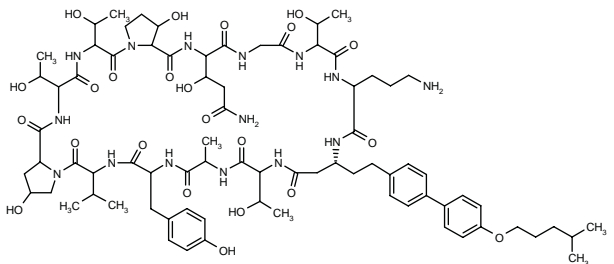
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1. Tanaka, T. et al. (Sankyo Co., Ltd.) *Anti-fungal agents containing triazole derivs.* JP 2000044547.

AEROTHRICIN 45

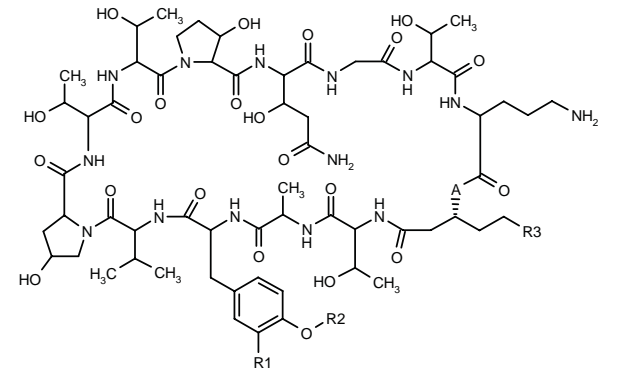
286710

DL-Threonyl-DL-alanyl-DL-tyrosyl-DL-valyl-DL-(4-hydroxy)prolyl-DL-threonyl-DL-threonyl-DL-(3-hydroxy)prolyl-DL-(2-hydroxy)glutaminy-glycyl-DL-threonyl-DL-ornithyl-[3-[2-[4'-(4-methylpentyl)oxy]biphenyl-4-yl]ethyl]]-β-D-alanine N-2.1-C-1.13-lactam



C78 H115 N15 O23; Mol wt: 1630.8490

ACTION – Antifungal agent obtained semisynthetically from a natural product isolated from *Deuteromycotina* sp. strain NR 7379 (FERM BP-6391), with potent *in vitro* activity against *Candida albicans* CY1002, *Aspergillus fumigatus* CF1003 and *Fusarium solani* CF1008 (IC₅₀ = 0.07, 0.08 and 2.30 µg/ml, respectively). *In vivo*, compound was shown to be effective in a murine model of systemic candidiasis (ED₅₀ = 0.3 mg/kg i.v. b.i.d. x 1 day followed by q.d. x 2 days). Compound exhibited weaker hepatic cytotoxicity as compared to known cyclic peptides such as LY-303366 and WF-11243 (aerothricin 3). Other compounds from this series of aerothricin analogues include the following:



Compound	R1	R2	R3	A	Formula
Aerothricin 5 [286711]	H	Me	C11H23	O	C72H118N14O23
Aerothricin 16 [286712]	NO2	H	C11H23	O	C71H115N15O25
Aerothricin 41 [286713]	H	H	4-[4-(C5H11O)-Ph]-Ph	NH	C77H113N15O23
Aerothricin 50 [286714]	H	H	6-(C6H13O)-2-Naph	NH	C76H113N15O23
Aerothricin 55 [286717]	NO2	H	4-[4-(C7H15)-Ph]-Ph	NH	C79H116N16O25

SOURCE – Roche.

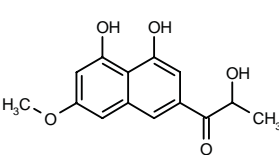
REFERENCES

1. Aoki, M. et al. (F. Hoffmann-La Roche AG) *Aerothricin analogs, their preparation and use.* WO 0005251.

CHAETOATROSIN A

287126

1-(4,5-Dihydroxy-7-methoxynaphthalen-2-yl)-2-hydroxypropan-1-one



C14 H14 O5; Mol wt: 262.2596

ACTION – Antifungal agent isolated from the culture broth of *Chaetomium atrobrunneum* F449, that acts by specifically inhibiting chitin synthase II (IC₅₀ = 104 µg/ml). It exhibited strong antifungal activity against the plant pathogen *Rhizoctonia solani* (MIC = 50 µg/ml) but was weakly active against *Trichophyton mentagrophytes* and *Cryptococcus neoformans* (MIC = 100 µg/ml) and inactive against *Candida albicans*, *Candida krusei* and *Coccidioides immitis* (MIC > 100 µg/ml). Potentially useful as a lead compound for the development of new antifungal agents acting through the control of chitin biosynthesis.

SOURCES – Chungnam National University, Taejon (KR); Korea Research Institute of Bioscience and Biotechnology, Taedok Science Town (KR).

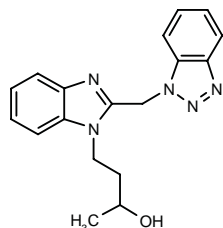
REFERENCES

1. Hwang, E.-I. et al. *Chaetoatrosin A, a novel chitin synthase II inhibitor produced by Chaetomium atrobrunneum F449.* J Antibiot 2000, 53(3): 248.

ANTIVIRAL DRUGS

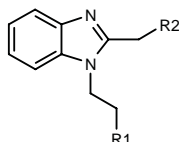
286220

4-[2-(1*H*-Benzotriazol-1-ylmethyl)-1*H*-benzimidazol-1-yl]butan-2-ol



C₁₈ H₁₉ N₅ O; Mol wt: 321.3821

ACTION – Antiviral agent with excellent activity against respiratory syncytial virus (RSV; 100% protection in HEP-2 cells infected with RSV Long strain at a concentration of 4 µg/ml vs. 100% protection for ribavirin at 2.5 µg/ml) and low cytotoxicity (CC₅₀ > 309 µM in uninfected cells vs. CC₅₀ = 40 µM for ribavirin). Other compounds from this series of substituted benzimidazole derivatives include the following:



Compound	R1	R2	Formula
286221	N(Me) ₂	1-benzotriazolyl	C ₁₈ H ₂₀ N ₆
286222	N(Me) ₃ ⁺ I ⁻	1-benzotriazolyl	C ₁₉ H ₂₃ N ₆
286223	SO ₂ Me	1-benzotriazolyl	C ₁₇ H ₁₇ N ₅ O ₂ S
286224	N(Me) ₂	2-benzotriazolyl	C ₁₈ H ₂₀ N ₆

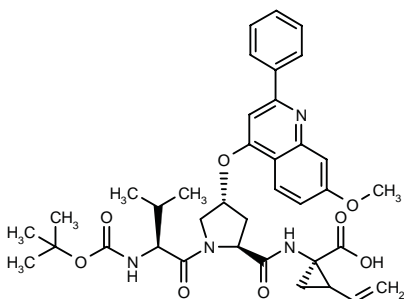
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Yu, K.-L. et al. (Bristol-Myers Squibb Co.) *Substd. benzimidazole antiviral agents*. WO 0004900.

286626

1(*R*)-[*N*-(*tert*-Butoxycarbonyl)-L-valyl-L-[4(*R*)-(7-methoxy-2-phenylquinolin-4-yloxy)]prolylamino]-2-vinylcyclopropanecarboxylic acid



C₃₇ H₄₄ N₄ O₈; Mol wt: 672.7746

ACTION – Hepatitis C virus (HCV) NS3 protease inhibitor (EC₅₀ = 8.2 µM in a cell-based assay) devoid of significant inhibitory activity against other serine proteases such as human leukocyte elastase (HLE), porcine pancreatic elastase (PPE) or bovine pancreatic chymotrypsin, or cysteine proteases such as human liver cathepsin B. It may furthermore be able to penetrate cell membranes and be active in cell culture, as well as having a good pharmacokinetic profile *in vivo*.

SOURCE – Boehringer Ingelheim.

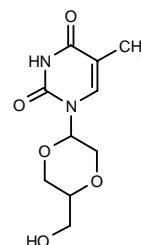
REFERENCES

1. Llinas-Brunet, M. et al. (Boehringer Ingelheim [Canada] Ltd.) *Hepatitis C inhibitor tripeptides*. WO 0009543.

286656

1-[5-(Hydroxymethyl)-1,4-dioxan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione

1-[5-(Hydroxymethyl)-1,4-dioxan-2-yl]thymine



C₁₀ H₁₄ N₂ O₅; Mol wt: 242.2296

ACTION – Nucleoside derivative with excellent activity against hepatitis B virus (HBV), giving EC₅₀ and EC₉₀ values against HBV in HepG2 cells of 4.5 and 15 µg/ml, respectively, versus a CC₅₀ value of 846 µg/ml (selectivity index = 188).

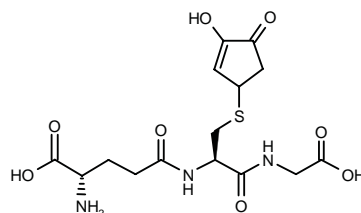
SOURCE – Chong Kun Dang.

REFERENCES

1. Kim, J.W. et al. (Chong Kun Dang Corp.) *Nucleoside derivs. and process for preparing thereof*. US 6034087, WO 9612716.

286772

δ-L-Glutamyl-L-[*S*-(3-hydroxy-4-oxocyclopent-2-en-1-yl)]cysteinyl-glycine



C₁₅ H₂₁ N₃ O₈ S; Mol wt: 403.4099

ACTION – Antiviral and carcinostatic agent, a representative compound from a series of cyclopentane and cyclopentene derivatives, proven active in mice infected with human influenza virus at 3 and 30 mg/kg i.p.

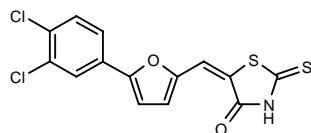
SOURCE – Takara Shuzo.

REFERENCES

1. Kobayashi, E. et al. (Takara Shuzo Co., Ltd.) *5-Membered ring cpds.* WO 0011021.

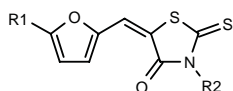
286817

5-[5-(3,4-Dichlorophenyl)furan-2-ylmethylene]-2-thioxo-thiazolidin-4-one



C₁₄ H₇ Cl₂ N O₂ S₂; Mol wt: 356.2523

ACTION – Antiviral agent for the treatment or prevention of infections and associated diseases caused by viruses of the Flaviviridae family; it inhibits virus-encoded RNA-dependent RNA polymerase (RdRp) protein of Flaviviridae including hepatitis C virus, *Pestivirus* and *Flavivirus* with IC₅₀ values of 1 μM or less. Other exemplified compounds include the following:



Compound	R1	R2	Formula
286818	3,4-(Cl) ₂ -Ph	CH ₂ CO ₂ H	C ₁₆ H ₉ Cl ₂ NO ₄ S ₂
286819	2-Cl-5-CF ₃ -Ph	CH(Me)CO ₂ H	C ₁₈ H ₁₁ ClF ₃ NO ₄ S ₂
286820	2-benzofuryl	4-CO ₂ H-Ph	C ₂₃ H ₁₃ NO ₅ S ₂

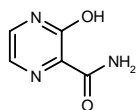
SOURCE – ViroPharma.

REFERENCES

1. Bailey, T.R. and Young, D.C. (ViroPharma, Inc.) *Cpds., compsns. and methods for treating or preventing viral infections and associated diseases.* WO 0010573.

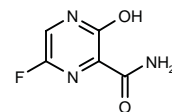
286833

3-Hydroxypyrazine-2-carboxamide



C₅ H₅ N₃ O₂; Mol wt: 139.1135

ACTION – Antiviral agent active against influenza virus, as demonstrated in a plaque reduction assay in MDCK cells infected with influenza virus A/PR/8/34 (91.9% inhibition at a concentration of 1 μg/ml), with low cytotoxicity (CC₅₀ = 250 μg/ml or more in uninfected Vero cells). Another compound from this series of heterocyclic carboxamide derivatives is:



286877: C₅ H₄ F N₃ O₂

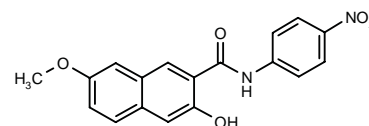
SOURCE – Toyama.

REFERENCES

1. Furuta, Y. and Egawa, H. (Toyama Chemical Co., Ltd.) *Nitrogenous heterocyclic carboxamide derivs. or salts thereof and antiviral agents containing both.* WO 0010569.

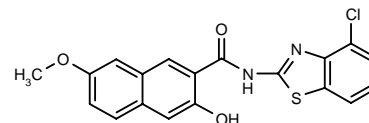
287365

3-Hydroxy-7-methoxy-*N*-(4-nitrophenyl)naphthalene-2-carboxamide



C₁₈ H₁₄ N₂ O₅; Mol wt: 338.3176

ACTION – Antiviral agent, a selective inhibitor of human cytomegalovirus (CMV) DNA polymerase (IC₅₀ = 1.5 μM). Another related compound is:



287364: C₁₉ H₁₃ Cl N₂ O₃ S

SOURCE – Pharmacia.

REFERENCES

1. Cudahy, M.M. et al. *Novel inhibitors of human cytomegalovirus.* 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 131.

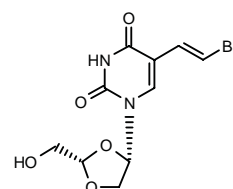
L-β-BV-OddU¹⁻⁴

280296

5-[(*E*)-2-Bromovinyl]-1-[2(*S*)-(hydroxymethyl)-1,3-dioxolan-4(*S*)-yl]pyrimidine-2,4(1*H*,3*H*)-dione

(*E*)-5-(2-Bromovinyl)-1-[2(*S*)-(hydroxymethyl)-1,3-dioxolan-4(*S*)-yl]uracil

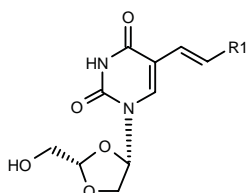
BCH-2639[†]



C₁₀ H₁₁ Br N₂ O₅; Mol wt: 319.1099

M.p. 176-8 °C; [α]_D²⁵ -4.6° (c 0.28, MeOH).

ACTION – Antiviral agent, a nucleoside analogue active against varicella-zoster virus ($IC_{50} = 0.06 \mu M$ for inhibition of virus replication in HEL cells), herpes simplex virus type 1 (HSV-1; $IC_{50} = 0.3 \mu g/ml$) and human cytomegalovirus ($IC_{50} = 5 \mu g/ml$). Compound did not show cytotoxicity in CEM cells at up to $200 \mu M$ and did not inhibit DNA synthesis. Within this series of (*E*)-5-(2-bromovinyl)uracil analogues, the following are also included:



Compound	R1	Formula
β-L-CV-OddU [288313]^{2,3}	Cl	C ₁₀ H ₁₁ ClN ₂ O ₅
β-L-IV-OddU [288314]^{2,3}	I	C ₁₀ H ₁₁ IN ₂ O ₅

SOURCES – University of Georgia, Athens, GA (US); Yale University, New Haven, CT (US).

REFERENCES

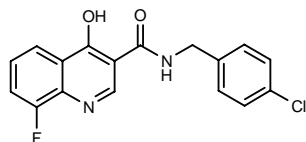
1. Bednarski, K. et al. *Inhibitory activities of herpes simplex viruses type 1 and 2 and human cytomegalovirus by stereoisomers of 2'-deoxy-3'-oxa-5(E)-(bromovinyl) uridines and their 4'-thio analogues*. Bioorg Med Chem Lett 1994, 4(22): 2667.
2. Choi, Y. et al. *Structure-activity relationships of L-dioxolane uracil nucleosides against varicella zoster virus*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 8.
3. Choi, Y.S. et al. *Structure-activity relationships of (E)-5-(2-bromovinyl) uracil and related pyrimidine L-nucleosides as antiviral agents for varicella zoster virus*. Antivir Res 2000, 46(1): Abst 149.
4. Li, L. et al. *Inhibition of the growth of varicella-zoster virus by L-β-5-bromovinyl-(2-hydroxymethyl)-L,3-dioxolanyluracil and its analogues*. Proc Amer Assoc Cancer Res 2000, 41: Abst 22.

[†]The title compound was referred to by this code name (BioChem Therapeutic, now BioChem Pharma) in Ref. 1.

PNU-145185

287340

N-(4-Chlorobenzyl)-8-fluoro-4-hydroxyquinoline-3-carboxamide



C₁₇ H₁₂ Cl F N₂ O₂; Mol wt: 330.7448

ACTION – Antiviral agent, a broad-spectrum inhibitor of herpesvirus DNA polymerases including human cytomegalovirus, herpes simplex virus and varicella-zoster virus polymerase ($IC_{50} = 3.6, 5.2$ and $1.1 \mu M$, respectively), with good selectivity over human α polymerase ($IC_{50} > 50 \mu M$).

SOURCE – Pharmacia.

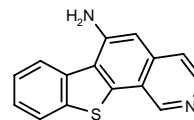
REFERENCES

1. Tucker, J.A. et al. (Pharmacia & Upjohn Co.) *4-Hydroxyquinoline-3-carboxamides and hydrazides as antiviral agents*. WO 9932450.
2. Vailancourt, V.A. et al. *4-Hydroxyquinoline-3-carboxamides as inhibitors of herpes virus DNA polymerases*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 135.

SR-10204*

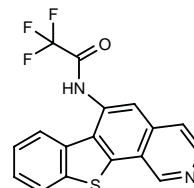
220850

6-Amino[1]benzothieno[3,2-*h*]isoquinoline



C₁₅ H₁₀ N₂ S; Mol wt: 250.3240

ACTION – Antiviral agent effective against human cytomegalovirus including both ganciclovir-sensitive ($IC_{50} = 0.4$ and $0.32 \mu M$ against laboratory strains and clinical isolates, respectively) and ganciclovir-resistant strains ($IC_{50} = 0.16-0.4 \mu M$); it was 30 times more potent than ganciclovir against sensitive strains and showed no activity against murine cytomegalovirus. Compound was also active when added to cells prior to virus adsorption, indicating that it may act either by preventing virus absorption or by targeting a viral function that occurs before or at the time of replication of viral DNA. Another representative compound within this series of benzo-thieno[3,2-*h*]isoquinolines is:



SR-10208 [223362]**: C₁₇ H₉ F₃ N₂ O S

SOURCE – SRI.

REFERENCES

1. Reist, E.J. (SRI International) *Novel benzothiophene analogs as antiviral agents*. EP 0712404, JP 1997500386, US 5424315, WO 9504059.
2. Zaveri, N. et al. *Benzothieno[3,2-*h*]isoquinolines as novel nonnucleoside inhibitors of human cytomegalovirus*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 130.

*Identified compound **220850** Drug Data Rep 1995, 017(07): 0657.

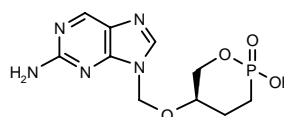
Identified compound **223362 (see **220850**) Drug Data Rep 1995, 017(07): 0657.

SR-3785

287249

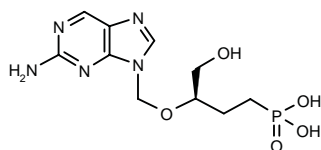
9-[(5*R*)-2-Hydroxy-2-oxo-1,2-oxaphosphorinan-5-yloxymethyl]-9*H*-purin-2-amine

5(*R*)-(2-Amino-9*H*-purin-9-ylmethoxy)-2-hydroxy-1,2-oxaphosphorinan-2-one



C₁₀ H₁₄ N₅ O₄ P; Mol wt: 299.2256

ACTION – Antiviral agent that inhibits the replication of murine (MCMV; IC_{50} = 1.8 μ g/ml) and human cytomegalovirus (HCMV; IC_{50} = 77, 31 and 6.7 μ g/ml, respectively, against strains AD-169, P8 and D16), being as potent as ganciclovir against strain D16 and showing relatively low cytotoxicity in MRC-5 cells (CD_{50} = 261-487 μ g/ml). In MCMV-infected mice, compound at a dose of 40 mg/kg i.p. increased survival from 0 of 20 in placebo-treated animals to 4 of 10 (40%) and slightly prolonged mean time to death to 8.3 ± 4.9 days from 6.4 ± 1.1 days on placebo. Another compound from this series of enantiomerically pure 2-aminopurine cyclic and acyclic nucleotide phosphonate analogues is:



SR-3784 [287248]: C₁₀ H₁₆ N₅ O₅ P

Although it showed no activity against HCMV, **SR-3784** was significantly more effective in MCMV-infected mice.

SOURCE – SRI.

REFERENCES

1. Reist, E.J. et al. (SRI International) *Enantiomerically pure 2-aminopurine phosphonate nucleotide analogs as antiviral agents*. US 5877166, WO 9741133.

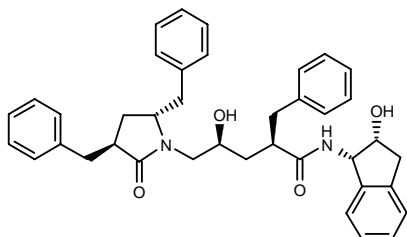
2. Zaveri, N. et al. *Enantiomerically pure 2-aminopurine cyclic and acyclic nucleotide phosphonate analogs as antiviral agents against human cytomegalovirus*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 129.

AIDS MEDICINES

GW-5950X*

254891

2(*R*)-Benzyl-5-[3(*R*),5(*R*)-dibenzyl-2-oxopyrrolidin-1-yl]-4(*S*)-hydroxy-*N*-[2(*R*)-hydroxyindan-1(*S*)-yl]pentanamide



C₃₉ H₄₂ N₂ O₄; Mol wt: 602.7810

ACTION – Anti-HIV agent, a heterocyclic isostere of the P1/P2 domain of amprenavir with subnanomolar activity against HIV-1 protease (K_i = 0.050 nM).

SOURCES – Glaxo Wellcome; Vertex.

REFERENCES

1. Tung, R.D. et al. (Vertex Pharmaceuticals Inc.) *Aspartyl protease inhibitors*. JP 2000501111, US 5945413, WO 9727180.

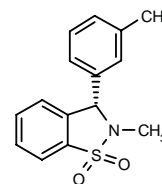
2. Kazmierski, W. et al. *Heterocyclic isosteres of the P1/P2 domain of amprenavir: Discovery of novel, picomolar HIV-1 protease inhibitors*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 126.

*Identified compound **254891** (see **254219**) Drug Data Rep 1997, 019(10): 0929.

NSC-708199

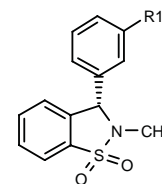
287460

(+)-2-Methyl-3(*S*)-(3-methylphenyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide



C₁₅ H₁₅ N O₂ S; Mol wt: 273.3545

ACTION – Anti-HIV agent, a non-nucleoside HIV-1 reverse transcriptase inhibitor (EC_{50} = 0.037 μ M). Other representative compounds within this series of 3-aryl-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxides, commonly known as sultams, are:



Compound	R1	Formula
NSC-701751 [287461]	Cl	C ₁₄ H ₁₂ ClNO ₂ S
NSC-703774 [287462]	Br	C ₁₄ H ₁₂ BrNO ₂ S
NSC-704673 [287463]	I	C ₁₄ H ₁₂ INO ₂ S

SOURCE – University of Tennessee, Knoxville, TN (US).

REFERENCES

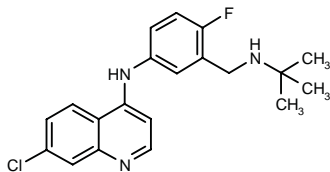
1. Baker, D.C. et al. (University of Tennessee Research Corporation) *Methods of synthesizing sultams and anti-viral compsns*. WO 0004004.

2. Condo, A.M. et al. *Synthesis and molecular modeling studies of 3-aryl-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxides: Nonnucleoside reverse transcriptase inhibitors of HIV-1*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 124.

TREATMENT OF PROTOZOAL DISEASES

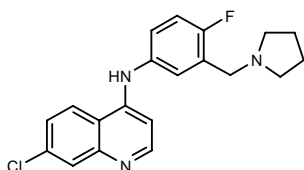
287246

N-[3-(*tert*-Butylaminomethyl)-4-fluorophenyl]-*N*-(7-chloroquinolin-4-yl)amine



C₂₀ H₂₁ Cl F N₃; Mol wt: 357.8579

ACTION – Antimalarial agent with potent activity against chloroquine-resistant strains of *Plasmodium falciparum*, as demonstrated by IC₅₀ values of 39 ± 5.5 and 20 ± 2.3 nM, respectively, against chloroquine-resistant and chloroquine-sensitive K1 and HB3 strains of *P. falciparum* vs. IC₅₀ values of 300 ± 2.3 and 35 ± 4.3 nM, respectively, for chloroquine and 20 ± 1.3 and 20 ± 7.3 nM, respectively, for amodiaquine. In addition, it exhibited potent antimalarial activity *in vivo* when tested in mice infected with *Plasmodium berghei* NS (ED₅₀ = 5.50 mg/kg vs. 10.71 mg/kg for amodiaquine). Compound is not liable to bioactivation *in vivo*, contrary to amodiaquine, and is thus expected to be devoid of toxic side effects. Another compound from this series of des-hydroxy-4-fluoro-amodiaquine derivatives is:



287247: C₂₀ H₁₉ Cl F N₃

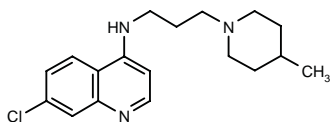
SOURCE – Ultrafine.

REFERENCES

- O'Neill, P.M. et al. (Ultrafine Ltd.) *Antimalarial cpds.* WO 0014070.

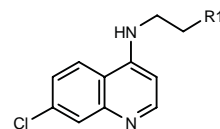
287336³

7-Chloro-*N*-[3-(4-methylpiperidin-1-yl)propyl]quinolin-4-amine



C₁₈ H₂₄ Cl N₃; Mol wt: 317.8616

ACTION – Antimalarial agent, a derivative of the modified aminoquinoline AQ-13 proven effective *in vitro* against chloroquine-susceptible, chloroquine-resistant and multidrug-resistant *Plasmodium falciparum*. Other related compounds are:



Compound	R1	Formula
AQ-13 [226963] ^{*,1,3}	CH ₂ N(Et) ₂	C ₁₆ H ₂₂ ClN ₃
287338 ³	1-Pip	C ₁₆ H ₂₀ ClN ₃
287339 ³	1-Pip-(CH ₂) ₁₀	C ₂₆ H ₄₀ ClN ₃

SOURCE – Tulane University, New Orleans, LA (US).

REFERENCES

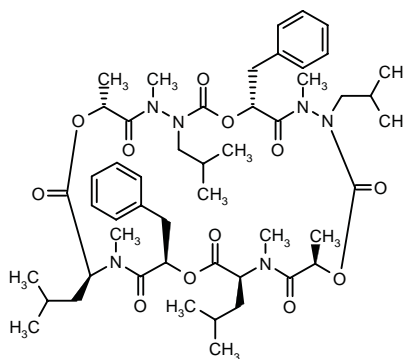
- Hofheinz, W. et al. (F. Hoffmann-La Roche AG) *Aminoquinoline derivatives useful in the treatment of malaria.* CA 2133620, EP 0656353, JP 1995188174, US 5596002.
- Cogswell, F.B. et al. *Pre-clinical studies of aminoquinolines active against chloroquine- and mefloquine-resistant Plasmodium falciparum.* Am J Trop Med Hyg 1997, 57(3, Suppl.): Abst 109.
- De, D. et al. *Modified aminoquinolines (AQS) with a terminal piperidine on the diaminoalkane side chain.* 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 1.

*Identified compound **226963** (see **224922**) Drug Data Rep 1995, 017(10): 0938.

TREATMENT OF HELMINTHIC DISEASES

287243

(6*R*,12*R*,15*S*,18*R*,21*S*,24*R*)-6,18-Dibenzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-3,4,9,10,16,22-hexaazacyclotetracosane-2,5,8,11,14,17,20,23-octone



C₅₀ H₇₄ N₆ O₁₂; Mol wt: 951.1646

ACTION – Anthelmintic agent active against endoparasites, with potent activity *in vitro* against *Trichinella spiralis* and *Nippostrongylus brasiliensis* at a concentration of 100 µg/ml. A representative compound from a series of azacyclodepsipeptides.

SOURCE – Bayer.

REFERENCES

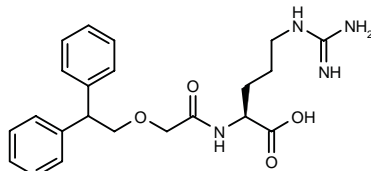
- Dyker, H. et al. (Bayer AG) *Azo-cyclodepsipeptides and their use as antiparasitics.* DE 19840320, WO 0014079.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

286580

N-[2-(2,2-Diphenylethoxy)acetyl]-L-arginine



C₂₂ H₂₈ N₄ O₄; Mol wt: 412.4872

ACTION – Complement C3a receptor antagonist with potential in the treatment of immune and inflammatory disorders associated with complement activation and/or increased levels of anaphylatoxins such as rheumatoid arthritis, Alzheimer's disease, psoriasis, gout, multiple sclerosis, systemic lupus erythematosus, glomerulonephritis and adult respiratory distress syndrome. A specifically claimed compound from a series of arginine derivatives.

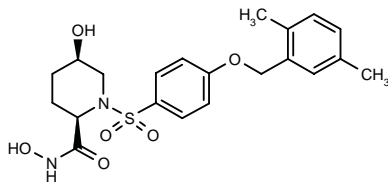
SOURCE – SmithKline Beecham.

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1. Lee, D. et al. (SmithKline Beecham Corp.) *C3A receptor ligands*. WO 0009129.

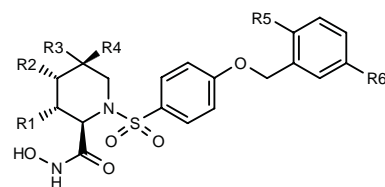
286581

1-[4-(2,5-Dimethylbenzyloxy)phenylsulfonyl]-5(*R*)-hydroxypiperidine-2(*R*)-carboxyhydroxamic acid



C₂₁ H₂₆ N₂ O₆ S; Mol wt: 434.5104

ACTION – Matrix metalloproteinase (MMP) inhibitor with differential activity against metalloproteinases and repolysins (ADAMs), preferably TACE (TNF- α -converting enzyme). Potentially useful in the treatment of arthritis, cancer and other conditions. Other specifically claimed hydroxy pipercolate hydroxamic acid derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
286583	H	H	H	OH	Me	F	C ₂₀ H ₂₃ FN ₂ O ₆ S
286584	H	OH	H	H	Me	H	C ₂₀ H ₂₄ N ₂ O ₆ S
286585	H	H	H	OH	Et	H	C ₂₁ H ₂₆ N ₂ O ₆ S
286587	H	OH	H	H	Me	Me	C ₂₁ H ₂₆ N ₂ O ₆ S
286588	H	H	Me	OH	i-Pr	H	C ₂₃ H ₃₀ N ₂ O ₆ S
286589	Me	H	H	OH	Me	H	C ₂₁ H ₂₆ N ₂ O ₆ S

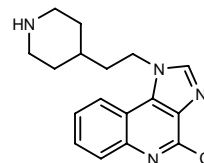
SOURCE – Pfizer.

REFERENCES

1. McClure, K.F. et al. (Pfizer Products Inc.) *Hydroxy pipercolate hydroxamic acid derivs. as MMP inhibitors*. WO 0009485.

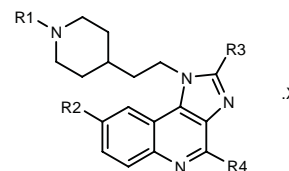
286649

4-Chloro-1-[2-(4-piperidinyl)ethyl]-1*H*-imidazo[4,5-*c*]-quinoline



C₁₇ H₁₉ Cl N₄; Mol wt: 314.8181

ACTION – Cytokine production inhibitor, particularly active against the production of TNF- α and IL-1 β , providing complete inhibition of lipopolysaccharide-stimulated TNF- α and IL-1 β production in human peripheral blood mononuclear cells at a concentration of 10 μ M. Potentially useful in the treatment or prevention of cytokine-mediated conditions. Other exemplified 1*H*-imidazopyridine derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
286650	CH ₂ Ph	H	H	NH ₂		C ₂₄ H ₂₇ N ₅
286651	H	H	Ph	Cl	fumarate, .HCl	C ₂₃ H ₂₃ ClN ₄ ·C ₄ H ₄ O ₄ ·ClH
286652	H	H	H	NH ₂	HCl	C ₁₇ H ₂₁ N ₅ ·ClH
286653	H	Cl	H	Cl		C ₁₇ H ₁₈ Cl ₂ N ₄
286654	H	H	CF ₃	Cl		C ₁₈ H ₁₈ ClF ₃ N ₄

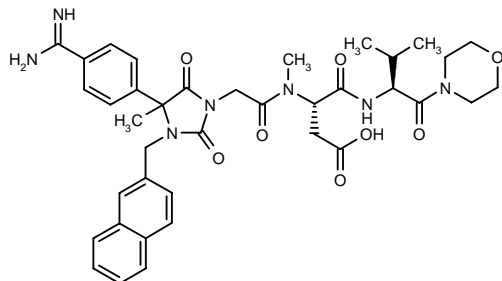
SOURCE – Hokuriku.

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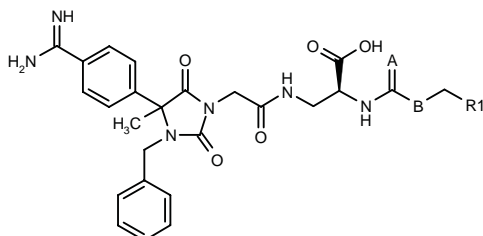
286657

3-(S)-[2-[4-(4-Amidinophenyl)-4-methyl-3-(naphthalen-2-ylmethyl)-2,5-dioximidazolidin-1-yl]-N-methylacetamido]-3-[N-[2-methyl-1-(S)-(morpholin-4-ylcarbonyl)propyl]-carbamoyl]propionic acid



C38 H45 N7 O8; Mol wt: 727.8145

ACTION – VLA-4 receptor antagonist and cell adhesion inhibitor found to potently inhibit the adhesion of human VCAM-1 to U937 cells ($IC_{50} = 0.73 \mu M$) as a measure of its ability to inhibit the interaction between VLA-4 and leukocytes. It is considered to be useful for the treatment or prophylaxis of rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, CNS inflammatory disorders, asthma, allergies, cardiovascular disorders, arteriosclerosis, restenosis and diabetes, as well as for protecting organ transplants, for inhibiting tumor growth and metastasis and in the treatment of malaria. Other exemplified heterocyclic compounds include the following:



Compound	R1	A	B	Formula
286658	1-adamantyl	O	O	$C_{38}H_{42}N_6O_7$
286659	Ph	O	NH	$C_{31}H_{33}N_7O_6$
286661	Ph	S	NH	$C_{31}H_{33}N_7O_5S$

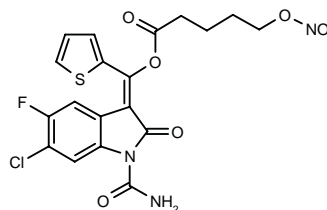
SOURCE – Aventis Pharma.

REFERENCES

1. Wehner, V. et al. (Aventis Pharma Deutschland GmbH) *Heterocyclic cpds., their preparation and their use as leucocyte adhesion inhibitors and VLA-4-antagonists*. DE 19741873, EP 0905139, US 6034238.

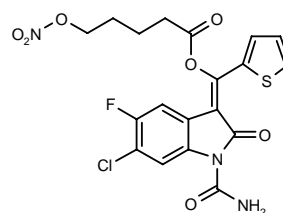
286731

5-(Nitrooxy)pentanoic acid (Z)-[1-(1-carbamoyl-6-chloro-5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-(2-thienyl)methyl] ester



C19 H15 Cl F N3 O7 S; Mol wt: 483.8585

ACTION – A representative compound from a series of nitric oxide (NO)-releasing oxindole prodrugs with analgesic and antiinflammatory properties; compounds of the invention are nonsteroidal antiinflammatory drugs* (NSAIDs) chemically linked to an NO donor in order to eliminate or reduce undesirable gastrointestinal side effects associated with said NSAIDs, thereby improving their therapeutic index. Another specifically claimed compound is:



286730: C19 H15 Cl F N3 O7 S

SOURCE – Pfizer.

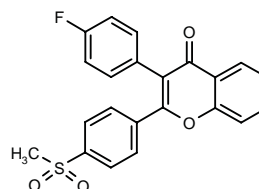
REFERENCES

1. Lundy, K.M. and Clark, M.T. (Pfizer Products Inc.) *Nitric oxide releasing oxindole prodrugs with analgesic and anti-inflammatory properties*. EP 0984012, JP 2000086629.

*See **Ilonidap** Drug Data Rep 1994, 016(010): 0881.

286759

3-(4-Fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-4H-1-benzopyran-4-one



C22 H15 F O4 S; Mol wt: 394.4205

ACTION – Antiinflammatory agent, a potent and selective cyclooxygenase type 2 (COX-2) inhibitor, as demonstrated by 94% inhibition of COX-2 activity at a concentration of 0.1 $\mu g/ml$ vs. < 5% inhibition of COX-1 at 10 $\mu g/ml$. *In vivo*, compound was shown to inhibit TPA-induced mouse ear edema, being equipotent to indomethacin ($ED_{50} = 0.4 \text{ mg/ear}$ for both), as well as carrageenan-induced mouse paw edema (43% inhibition at 50 mg/kg p.o. vs. $ED_{50} = 4.3 \text{ mg/kg p.o.}$ for indomethacin). A representative compound from a series of diarylbenzopyran derivatives.

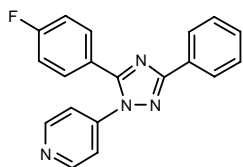
SOURCE – Pacific Corp.

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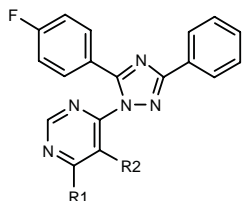
286792

4-[5-(4-Fluorophenyl)-3-phenyl-1*H*-1,2,4-triazol-1-yl]pyridine



C19 H13 F N4; Mol wt: 316.3377

ACTION – CSBP/RK/p38 kinase inhibitor with potential in the treatment of arthritic conditions, septic shock, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disorders, osteoporosis, restenosis, cardiac and renal reperfusion injury, chronic renal failure, congestive heart failure, angiogenic disorders, thrombosis, graft-vs.-host reaction, allograft rejection, inflammatory bowel disease, diabetes, multiple sclerosis, eczema, psoriasis and conjunctivitis. Other specifically claimed compounds from this series of substituted triazole derivatives include the following:



Compound	R1	R2	Formula
286793	NH2	H	C ₁₈ H ₁₃ FN ₆
286794	-CH=C(OMe)C(OMe)=CH-		C ₂₄ H ₁₈ FN ₅ O ₂

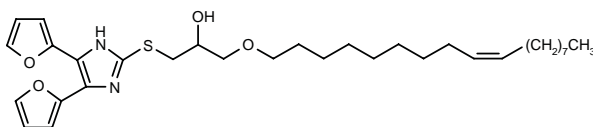
SOURCE – SmithKline Beecham.

REFERENCES

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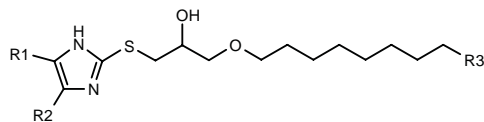
286924

1-[4,5-Bis(furan-2-yl)-1*H*-imidazol-2-ylsulfanyl]-3-[9(*Z*)-octadecenyoxy]propan-2-ol

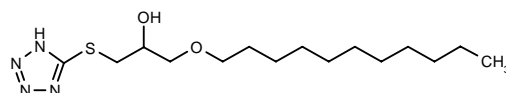


C32 H48 N2 O4 S; Mol wt: 556.8072

ACTION – Cytoplasmic phospholipase A₂ (cPLA₂) inhibitor (IC₅₀ = 0.5 μM) with potential for the treatment of inflammatory, autoimmune and allergic diseases, as well as for use as an antipyretic and analgesic agent. Other compounds from this series of thio-1,2-propanediol derivatives include the following:



Compound	R1	R2	R3	Formula
286925	2-Pyr	2-Pyr	C10H21	C ₃₄ H ₅₂ N ₄ O ₂ S
286926	2-furyl	2-furyl	C10H21	C ₃₂ H ₅₀ N ₂ O ₄ S
286927	3-furyl	3-furyl	Pr	C ₂₅ H ₃₆ N ₂ O ₄ S
286929	2-furyl	H	(<i>Z</i>)-CH=CHC8H17	C ₂₈ H ₄₆ N ₂ O ₃ S



286928: C15 H30 N4 O2 S

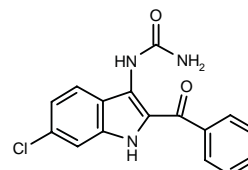
SOURCE – Japan Energy.

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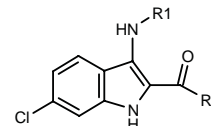
286987

N-(2-Benzoyl-6-chloro-1*H*-indol-3-yl)urea



C16 H12 Cl N3 O2; Mol wt: 313.7428

ACTION – Antiinflammatory agent, a selective cyclooxygenase type 2 (COX-2) inhibitor for the treatment of pain, inflammation and inflammation-related disorders such as arthritis. Other specifically claimed compounds within this series of substituted indole derivatives include the following:



Compound	R1	R2	Formula
286988	CONH2	3-Me-Ph	C ₁₇ H ₁₄ ClN ₃ O ₂
286989	CON(Me)OMe	Ph	C ₁₈ H ₁₆ ClN ₃ O ₃
286990	CON(Me)OMe	3-(CH2OH)-2-furyl	C ₁₇ H ₁₆ ClN ₃ O ₅
286993	SO2Me	Ph	C ₁₆ H ₁₃ ClN ₂ O ₃ S
286994	SO2Me	3-Me-Ph	C ₁₇ H ₁₅ ClN ₂ O ₃ S
286995	SO2Me	3-Cl-Ph	C ₁₆ H ₁₂ Cl ₂ N ₂ O ₃ S
286996	SO2Me	3-Br-Ph	C ₁₆ H ₁₂ BrClN ₂ O ₃ S

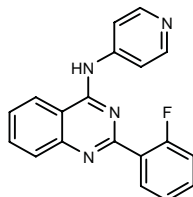
SOURCE – Pfizer.

REFERENCES

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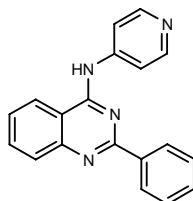
287081

2-(2-Fluorophenyl)-N-(4-pyridyl)quinazolin-4-amine



C19 H13 F N4; Mol wt: 316.3377

ACTION – An inhibitor of p38 α kinase and/or transforming growth factor- β (TGF- β) activity, with potential in the treatment of inflammatory or fibroproliferative disorders such as rheumatoid arthritis, osteoarthritis, multiple sclerosis, septic shock, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, psoriasis, restenosis, bone resorption disorders, graft-versus-host reaction, Crohn's disease, ulcerative colitis and fever. *In vitro*, compound inhibited p38 α kinase activity with an IC₅₀ in the range of 0.1-1.5 μ M, showing good selectivity as regards other kinases such as p38 γ , JNK1, PKC (protein kinase C) and EGF (epidermal growth factor) receptor kinase (IC₅₀ = 227, 167, > 100 and 4.2 μ M, respectively). Another exemplified compound from this series of quinazoline derivatives is:



287082: C19 H14 N4

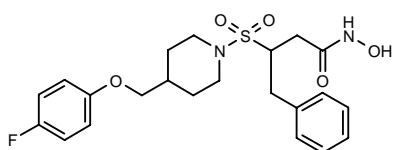
SOURCE – Scios.

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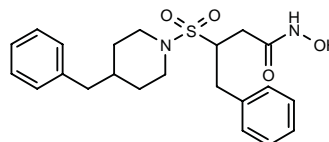
287097

3-[4-(4-Fluorophenoxymethyl)piperidin-1-ylsulfonyl]-4-phenylbutyroxamic acid



C22 H27 F N2 O5 S; Mol wt: 450.5283

ACTION – Matrix metalloproteinase (MMP) inhibitor with potential in the treatment of rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, gingivitis, corneal or gastric ulceration, ulcerative colitis, Crohn's disease, pressure sores, tumor metastasis, invasion or growth, multiple sclerosis, psoriasis, proliferative retinopathies, neovascular glaucoma, hemangiomas, cerebral or cardiac infarction and for wound healing. Another specifically claimed compound from this series of hydroxamic acid derivatives is:



287098: C22 H28 N2 O4 S

SOURCE – British Biotech.

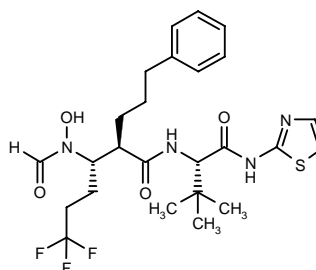
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1. Martin, F.M. (British Biotech Pharmaceuticals Ltd.) *Hydroxamic acid derivs. as proteinase inhibitors*. WO 0012477.

287118

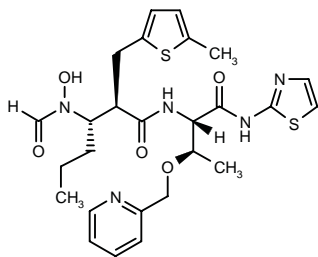
N-[2,2-Dimethyl-1(S)-[N-(2-thiazolyl)carbamoyl]propyl]-6,6,6-trifluoro-3(S)-(N-hydroxyformamido)-2(R)-(3-phenylpropyl)hexanamide

2(S)-[6,6,6-Trifluoro-3(S)-(N-formyl-N-hydroxyamino)-2(R)-(3-phenylpropyl)hexanamido]-3,3-dimethyl-N-(2-thiazolyl)butyramide



C25 H33 F3 N4 O4 S; Mol wt: 542.6197

ACTION – Potent, orally active inhibitor of matrix metalloproteinases (MMPs), TNF- α release from monocytes via inhibition of TNF- α -converting enzyme (TACE), shedding of cell-surface protein ectodomains and CD23 proteolysis, with potential for inhibiting the growth of tumor metastases and for the treatment of arthritis, diabetes and periodontal disease. *In vitro*, compound inhibited collagenase 3 and gelatinase B with K_i values < 100 nM, and TACE and stromelysin 1 with K_i values of 100-500 nM, while it was inactive against collagenase 1 (K_i > 1 μ M). When tested *in vivo* in mice, it produced 50-75% inhibition of the lipopolysaccharide-stimulated elevation in serum TNF- α levels at a dose of 40 mg/kg p.o. Another compound from this series of formamide derivatives is:



287119: C26 H33 N5 O5 S2

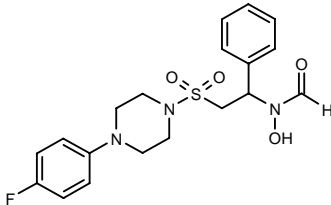
SOURCE – Glaxo Wellcome.

REFERENCES

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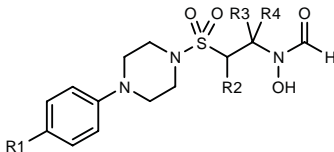
287145

N-[2-[4-(4-Fluorophenyl)piperazin-1-ylsulfonyl]-1-phenylethyl]-*N*-hydroxyformamide

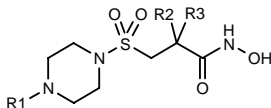


C19 H22 F N3 O4 S; Mol wt: 407.4638

ACTION – An inhibitor of matrix metalloproteinases (MMPs), particularly MMP-13 (collagenase 3) and MMP-9 (gelatinase B), with potential in the treatment of arthritis and atherosclerosis. Other exemplified compounds from this series of arylpiperazines include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
287146	F	H	CH2CH2Ph	H		C ₂₁ H ₂₆ FN ₃ O ₄ S
287147	F	H	cyclopentyl	H		C ₁₈ H ₂₆ FN ₃ O ₄ S
287148	F	H	3,4-(Cl)2-Ph	H		C ₁₉ H ₂₀ Cl ₂ FN ₃ O ₄ S
287149	F	H	-(CH2)5-			C ₁₈ H ₂₆ FN ₃ O ₄ S
287154	H	H	Ph	H		C ₁₉ H ₂₃ N ₃ O ₄ S
287155	F	H	4-quinolyl	H		C ₂₂ H ₂₃ FN ₃ O ₄ S
287156	F	Pr	3,4-(Cl)2-Ph	H		C ₂₂ H ₂₆ Cl ₂ FN ₃ O ₄ S
287157	F		-(CH2)4-	H	trans	C ₁₇ H ₂₄ FN ₃ O ₄ S
287158	F		-(CH2)4-	H	cis	C ₁₇ H ₂₄ FN ₃ O ₄ S



Compound	R1	R2	R3	Formula
287150	4-F-Ph	H	H	C ₁₃ H ₁₈ FN ₃ O ₄ S
287151	CH2Ph	H	H	C ₁₄ H ₂₁ N ₃ O ₄ S
287152	4-F-Ph	H	i-Bu	C ₁₇ H ₂₆ FN ₃ O ₄ S
287153	4-F-Ph	-(CH2)5-		C ₁₈ H ₂₆ FN ₃ O ₄ S

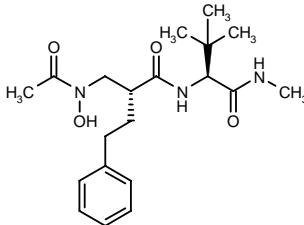
SOURCE – AstraZeneca.

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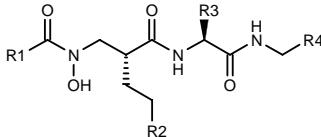
287166

*N*²-[2(*R*)-(N-Hydroxyacetamidomethyl)-4-phenylbutyryl]-*N*¹-methyl-L-*tert*-leucinamide



C20 H31 N3 O4; Mol wt: 377.4819

ACTION – An inhibitor of matrix metalloproteinases (MMPs), particularly MMP-13 (collagenase 3), with potential in the treatment of inflammatory and allergic conditions. Other exemplified compounds from this series of *N*-hydroxyacylamino derivatives include the following:



Compound	R1	R2	R3	R4	Formula
287167	Et	Ph	t-Bu	H	C ₂₁ H ₃₃ N ₃ O ₄
287168	i-Pr	Ph	t-Bu	H	C ₂₂ H ₃₅ N ₃ O ₄
287169	Ph	Ph	t-Bu	H	C ₂₅ H ₃₃ N ₃ O ₄
287170	CH2CH2Ph	CH2Ph	cyclohexyl-CH2	CH2Ph	C ₃₈ H ₄₉ N ₃ O ₄
287171	Me	4-F-Ph-CH2CH2	cyclohexyl-CH2	CH2Ph	C ₃₂ H ₄₄ FN ₃ O ₄

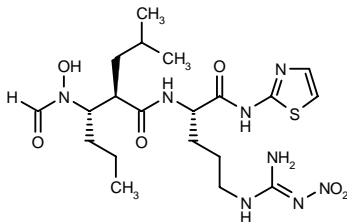
SOURCE – AstraZeneca.

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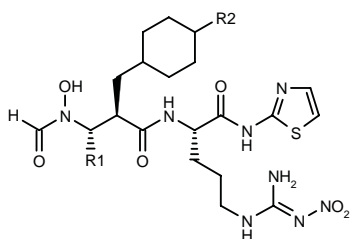
287172

N^α-[3(*S*)-(N-Formyl-N-hydroxyamino)-2(*R*)-isobutylhexanoyl]-*N*^{ω'}-nitro-*N*¹-(2-thiazolyl)-L-argininamide



C20 H34 N8 O6 S; Mol wt: 514.6046

ACTION – An inhibitor of matrix metalloproteinases (MMPs), as well as of TNF- α release from monocytes via inhibition of TNF- α -converting enzyme (TACE), shedding of cell-surface protein ectodomains and of CD23 proteolysis, potentially useful for inhibiting the growth of tumor metastases and for the treatment of arthritis, diabetes and periodontal disease. *In vitro*, compound was shown to inhibit TACE, collagenase 1, collagenase 3, gelatinase B, stromelysin 1 and TNF- α release from lipopolysaccharide (LPS)/PMA-stimulated monocytes with K_i/IC_{50} values < 50 nM. When tested *in vivo* in mice, it inhibited the LPS-induced elevation in serum TNF- α levels by > 75% at a dose of 40 mg/kg s.c. Other compounds from this series of formamide derivatives include the following:



Compound	R1	R2	Formula
287173	Pr	H	C ₂₃ H ₃₈ N ₈ O ₆ S
287174	CH ₂ CH ₂ CF ₃	H	C ₂₃ H ₃₅ F ₃ N ₈ O ₆ S
287175	Pr	Me	C ₂₄ H ₄₀ N ₈ O ₆ S
287176	i-Pr	Me	C ₂₄ H ₄₀ N ₈ O ₆ S
287177	cyclopropyl	H	C ₂₃ H ₃₈ N ₈ O ₆ S

SOURCE – Glaxo Wellcome.

REFERENCES

- Andrews, R.C. et al. (Glaxo Group Ltd.) *Formamide cpds. as therapeutic agents*. WO 0012466.

IMMUNOMODULATING AGENTS

286749

Recombinant multivalent malarial vaccine comprising peptides derived from different stages in the life cycle of Plasmodium falciparum

ACTION – Recombinant multivalent malaria vaccine that comprises an antigenic recombinant protein prepared by constructing a gene that encodes antigenic determinants from different stages in the life cycle of the parasite *Plasmodium falciparum*. The various stages covered by the vaccine are the sporozoite stage, the liver stage, the blood stage and the sexual stage (also known as the gametocyte stage). The gene produces a single protein that confers immunity against the different stages of the life cycle and thus provides a multivalent and multistage vaccine for malaria caused by *P. falciparum*.

SOURCES – Department of Health & Human Services (US); National Institute of Immunology, New Delhi (IN).

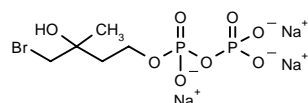
REFERENCES

- Lal, A.A. et al. (Department of Health & Human Services; National Institute of Immunology) *Recombinant multivalent malarial vaccine against Plasmodium falciparum*. WO 0011179.

286954

Diphosphoric acid 4-bromo-3-hydroxy-3-methylbutyl ester trisodium salt

BrHPP sodium salt



C₅ H₁₀ Br Na₃ O₈ P₂; Mol wt: 408.9480

ACTION – Immunomodulating agent for the treatment of cancer, infectious diseases caused by mycobacteria, parasites and protozoa, and AIDS that acts by stimulating the activation of T γ 9 δ 2 (also known as T γ 2 δ 2) lymphocytes. When tested *in vitro*, compound was found to be more potent than the natural phosphoantigen isopentenyl pyrophosphate (IPP) in activating the production of T γ 9 δ 2 lymphocytes in a culture of T-lymphocytes from human blood in the presence of human IL-12 (ED₅₀ = 10 nM vs. 3000 nM for IPP). When tested *in vivo* in monkeys at 0.1 mg/kg i.v. in combination with IL-12, a significant increase in the proliferation and activation of T γ 9 δ 2 lymphocytes was also observed. No toxicity was seen following i.v. administration of 1 mg to mice. A representative compound from a series of phosphohalohydrin derivatives.

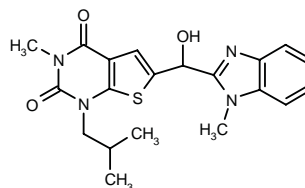
SOURCE – INSERM, Paris Cedex (FR).

REFERENCES

- Belmant, C. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale]) *Phosphohalohydrins, method for making same and uses*. FR 2782721, WO 0012516.

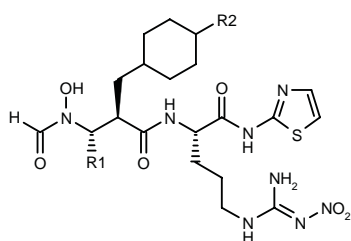
287059

6-[1-Hydroxy-1-(1-methyl-1H-benzimidazol-2-yl)methyl]-1-isobutyl-3-methylthieno[2,3-d]pyrimidine-2,4(1H,3H)-dione



C₂₀ H₂₂ N₄ O₃ S; Mol wt: 398.4848

ACTION – An inhibitor of matrix metalloproteinases (MMPs), as well as of TNF- α release from monocytes via inhibition of TNF- α -converting enzyme (TACE), shedding of cell-surface protein ectodomains and of CD23 proteolysis, potentially useful for inhibiting the growth of tumor metastases and for the treatment of arthritis, diabetes and periodontal disease. *In vitro*, compound was shown to inhibit TACE, collagenase 1, collagenase 3, gelatinase B, stromelysin 1 and TNF- α release from lipopolysaccharide (LPS)/PMA-stimulated monocytes with K_i/IC_{50} values < 50 nM. When tested *in vivo* in mice, it inhibited the LPS-induced elevation in serum TNF- α levels by > 75% at a dose of 40 mg/kg s.c. Other compounds from this series of formamide derivatives include the following:



Compound	R1	R2	Formula
287173	Pr	H	C ₂₃ H ₃₈ N ₈ O ₆ S
287174	CH ₂ CH ₂ CF ₃	H	C ₂₃ H ₃₅ F ₃ N ₈ O ₆ S
287175	Pr	Me	C ₂₄ H ₄₀ N ₈ O ₆ S
287176	i-Pr	Me	C ₂₄ H ₄₀ N ₈ O ₆ S
287177	cyclopropyl	H	C ₂₃ H ₃₈ N ₈ O ₆ S

SOURCE – Glaxo Wellcome.

REFERENCES

1. Andrews, R.C. et al. (Glaxo Group Ltd.) *Formamide cpds. as therapeutic agents*. WO 0012466.

IMMUNOMODULATING AGENTS

286749

Recombinant multivalent malarial vaccine comprising peptides derived from different stages in the life cycle of Plasmodium falciparum

ACTION – Recombinant multivalent malaria vaccine that comprises an antigenic recombinant protein prepared by constructing a gene that encodes antigenic determinants from different stages in the life cycle of the parasite *Plasmodium falciparum*. The various stages covered by the vaccine are the sporozoite stage, the liver stage, the blood stage and the sexual stage (also known as the gametocyte stage). The gene produces a single protein that confers immunity against the different stages of the life cycle and thus provides a multivalent and multistage vaccine for malaria caused by *P. falciparum*.

SOURCES – Department of Health & Human Services (US); National Institute of Immunology, New Delhi (IN).

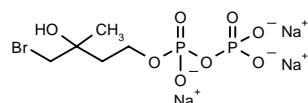
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286954

Diphosphoric acid 4-bromo-3-hydroxy-3-methylbutyl ester trisodium salt

BrHPP sodium salt



C₅ H₁₀ Br Na₃ O₈ P₂; Mol wt: 408.9480

ACTION – Immunomodulating agent for the treatment of cancer, infectious diseases caused by mycobacteria, parasites and protozoa, and AIDS that acts by stimulating the activation of T γ 9 δ 2 (also known as T γ 2 δ 2) lymphocytes. When tested *in vitro*, compound was found to be more potent than the natural phosphoantigen isopentenyl pyrophosphate (IPP) in activating the production of T γ 9 δ 2 lymphocytes in a culture of T-lymphocytes from human blood in the presence of human IL-12 (ED₅₀ = 10 nM vs. 3000 nM for IPP). When tested *in vivo* in monkeys at 0.1 mg/kg i.v. in combination with IL-12, a significant increase in the proliferation and activation of T γ 9 δ 2 lymphocytes was also observed. No toxicity was seen following i.v. administration of 1 mg to mice. A representative compound from a series of phosphohalohydrin derivatives.

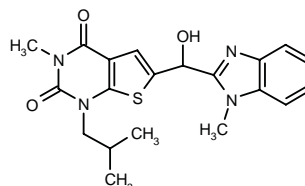
SOURCE – INSERM, Paris Cedex (FR).

REFERENCES

1. Belmant, C. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale]) *Phosphohalohydrins, method for making same and uses*. FR 2782721, WO 0012516.

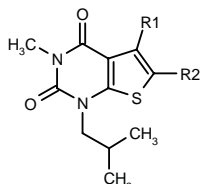
287059

6-[1-Hydroxy-1-(1-methyl-1H-benzimidazol-2-yl)methyl]-1-isobutyl-3-methylthieno[2,3-d]pyrimidine-2,4(1H,3H)-dione



C₂₀ H₂₂ N₄ O₃ S; Mol wt: 398.4848

ACTION – Immunosuppressive agent, a specifically claimed compound within a series of thieno[2,3-*d*]-pyrimidine-2,4-dione derivatives with potential in the treatment or prevention of autoimmune, inflammatory, proliferative and hyperproliferative diseases, particularly reversible obstructive airways diseases. *In vitro*, compound inhibited PMA/ionomycin-stimulated human peripheral blood mononuclear cell (PBMC) proliferation with an IA_{50} value of $< 1 \mu M$. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
287060	H	2-thienyl-CH(OH)	$C_{18}H_{18}N_2O_3S_2$
287061	H	4-Cl-1-Me-3-pyrazolyl-CH(OH)	$C_{16}H_{19}ClN_4O_3S$
287062	H	1-benzimidazolyl-CH2	$C_{19}H_{20}N_4O_2S$
287063	H	2-benzothiazolyl-CH2	$C_{19}H_{20}N_4O_2S$
287065	2-thienyl-S	3-Pyr-CO	$C_{21}H_{19}N_3O_3S_3$
287066	i-PrS	3-Pyr-CO	$C_{20}H_{23}N_3O_3S_2$
287067	i-PrS	3-oxo-2,3-dihydro-1,2-benzisothiazol-2-yl-CH2	$C_{22}H_{25}N_3O_5S_3$

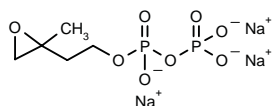
SOURCE – AstraZeneca.

REFERENCES

- Bantick, J. et al. (Astra Pharmaceuticals, Ltd.; Astra AB) *Novel cpds.* WO 0012514.

287121

Diphosphoric acid 3,4-epoxy-3-methylbutyl ester trisodium salt



C5 H9 Na3 O8 P2; Mol wt: 328.0361

ACTION – Immunomodulating agent for the treatment of cancer, infectious diseases caused by mycobacteria, parasites and protozoa, and AIDS that acts by stimulating the activation of $T\gamma 9\delta 2$ (also known as $T\gamma 2\delta 2$) lymphocytes. When tested *in vitro*, compound was found to be more potent than the natural phosphoantigen isopentenyl pyrophosphate (IPP) in activating the production of $T\gamma 9\delta 2$ lymphocytes in a culture of T-lymphocytes from human blood in the presence of human IL-12 ($ED_{50} = 20 \text{ nM}$ vs. 3000 nM for IPP). No toxicity was observed following i.v. administration of 1 mg to mice. A representative compound from a series of phosphoepoxide derivatives.

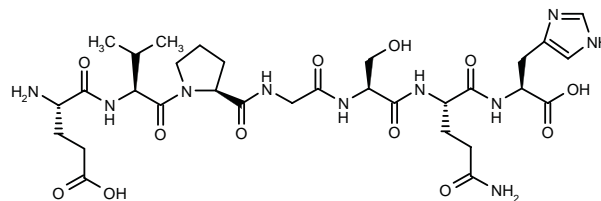
SOURCE – INSERM, Paris Cedex (FR).

REFERENCES

- Belmant, C. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale]) *Phosphoepoxides, method for making same and uses.* FR 2782722, WO 0012519.

287214

L-Glutamyl-L-valyl-L-prolyl-glycyl-L-seryl-L-glutaminy-L-histidine



C31 H48 N10 O12; Mol wt: 752.7782

ACTION – Peptide fragment of cholera toxin B (CtxB) or enterotoxin B (EtxB) that exhibits similar activity to CtxB and/or EtxB but lacks ganglioside GM_1 receptor-binding activity, claimed for use as an immunomodulator or as an adjuvant, as well as for the treatment of toxin-induced diarrhea.

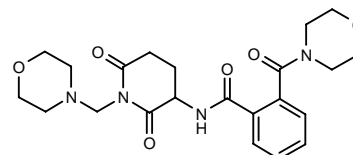
SOURCE – University of Bristol, Bristol (GB).

REFERENCES

- Williams, N.A. and Hirst, T.R. (University of Bristol) *Peptide fragments of cholera toxin B or enterotoxin B as vaccine adjuvants.* WO 0014114.

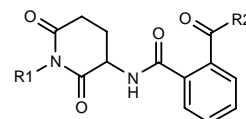
287706

2-(4-Morpholinylcarbonyl)-*N*-[1-(4-morpholinylmethyl)-2,6-dioxopiperidin-3-yl]benzamide



C22 H28 N4 O6; Mol wt: 444.4852

ACTION – Immunomodulator found to modulate the IL-10/IL-12 balance, as demonstrated in lipopolysaccharide-activated human monocytes by an increase in IL-10 production and a decrease in IL-12 synthesis (127 and 30%, respectively, at $10 \mu g/ml$ vs. 100% for controls). This profile makes it useful for the treatment of inflammatory and autoimmune diseases. Other exemplified substituted benzamides are:



Compound	R1	R2	Formula
287707	OH	OMe	$C_{14}H_{14}N_2O_6$
287708	4-Pip-CH2	4-morpholinyl	$C_{23}H_{30}N_4O_5$
287709	1-Pip-CH2	OEt	$C_{21}H_{27}N_3O_5$

SOURCE – Grünenthal.

REFERENCES

- Frosch, S. et al. (Grünenthal GmbH) *Substd. benzamides and their use as immunomodulators.* EP 0989121, JP 2000095761.

BASB024

286750

Polypeptides of Neisseria meningitidis

ACTION – BASB024 polypeptides of *Neisseria meningitidis* and polynucleotides encoding them, useful in vaccines against bacterial infections caused by this organism, preferably for genetic immunization. Diagnostic methods for diseases associated with *N. meningitidis*, detecting the expression of BASB024 polynucleotides, are also claimed.

SOURCE – SmithKline Beecham.

REFERENCES

1. Thonnard, J. (SmithKline Beecham Biologicals SA) *BASB024 outer membrane protein of Neisseria meningitidis*. WO 0011182.

BASB033

287962

Polypeptides of Neisseria meningitidis

ACTION – BASB033 polypeptides of *Neisseria meningitidis* and polynucleotides encoding them, useful in vaccines against bacterial infections caused by this organism, preferably for genetic immunization. Diagnostic methods for diseases associated with *N. meningitidis*, detecting the expression of BASB033 polynucleotides, are also claimed.

SOURCE – SmithKline Beecham.

REFERENCES

1. Ruelle, J.-L. (SmithKline Beecham Biologicals SA) *Polynucleotides and polypeptides BASB033 from Neisseria meningitidis and their uses*. WO 0015801.

BASB034

287967

Polypeptides of Moraxella catarrhalis

ACTION – BASB034 polypeptides of *Moraxella catarrhalis* and polynucleotides encoding them, useful in vaccines against bacterial infections caused by this organism, preferably for genetic immunization. Diagnostic methods for diseases associated with *M. catarrhalis*, detecting the expression of BASB034 polynucleotides, are also claimed.

SOURCE – SmithKline Beecham.

REFERENCES

1. Ruelle, J.-L. (SmithKline Beecham Biologicals SA) *Moraxella catarrhalis BASB034 polypeptides and uses thereof*. WO 0015802.

CSIMM-1

286715

Human cell-surface immunomodulator polypeptide with 335 amino acids

ACTION – Human cell-surface immunomodulator (CSIMM), a polypeptide expressed in cells derived from tissues associated with cancer, inflammation and the immune system that appears to be associated with cancer and immune disorders. Polynucleotides encoding this polypeptide, as well as expression vectors, agonists, antibodies and antagonists, are also provided. It is potentially useful in the diagnosis and treatment of cancer and immune diseases. Another CSIMM polypeptide is:

Human cell-surface immunomodulator polypeptide with 250 amino acids

CSIMM-2 [286716]

SOURCE – Incyte.

REFERENCES

1. Lal, P. et al. (Incyte Pharmaceuticals, Inc.) *Cell surface immunomodulators*. WO 0011150.

INTERLEUKIN-1ε

286762

Human interleukin-1ε polypeptide

hIL-1ε

ACTION – Human polypeptide from the IL-1 family that is believed to be involved in the generation and maintenance of immune and inflammatory responses and in protection against infection. Polynucleotides encoding this polypeptide, as well as expression vectors, antibodies, agonists and antagonists thereof, are also disclosed.

SOURCE – Immunex.

REFERENCES

1. Sims, J.E. and Smith, D.E. (Immunex Corp.) *Human IL-1 epsilon DNA and polypeptides*. WO 0011174.

PNEUMOCOCCAL 7-VALENT CONJUGATE VACCINE*

261651

Heptavalent pneumococcal vaccine composed of saccharides of capsular antigens of Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F individually conjugated to diphtheria CRM197 protein via reductive amination and combined into the 7-valent formulation

PNCRM197

PNCRM7⁺

ACTION – Pneumococcal 7-valent conjugate vaccine.

INDICATION – Active immunization of infants and toddlers against invasive disease caused by *Streptococcus pneumoniae* due to capsular serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F and 23F).

PRESENTATION – Vials, suspension for i.m. injection, 0.5 ml formulated to contain 2 µg of each saccharide for serotypes 4, 9V, 14, 18C, 19F and 23F, and 4 µg of 6B per dose (16 µg total saccharides), approximately 20 µg of CRM197 carrier protein and 0.125 mg aluminum as aluminum phosphate adjuvant.

PROPRIETARY NAME – *Prevnar* (US).

SOURCE – Wyeth-Ayerst.

REFERENCES

1. Black, S. et al. *Efficacy of heptavalent conjugate pneumococcal vaccine (Wyeth Lederle) in 37,000 infants and children: Impact of pneumonia, otitis media, and an update on invasive disease - Results of the Northern California Kaiser Permanente efficacy trial.* 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst G1398.
2. Black, S. et al. *Efficacy of heptavalent conjugate pneumococcal vaccine (Wyeth Lederle) in 37,000 infants and children: Results of the Northern California Kaiser Permanente efficacy trial.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst LB-9.
3. Black, S. et al. *Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children.* *Pediatr Infect Dis J* 2000, 19(3): 187.
4. Choo, S. et al. *Immunogenicity and safety of a pneumococcal conjugate vaccine combined with a Hib vaccine in UK infants.* 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst G248.
5. Edwards, K.M. et al. *Carriage of pneumococci among infants immunized with a 9-valent pneumococcal (Pnc) conjugate vaccine at 2, 4, and 6 months of age.* 37th Annu Meet Infect Dis Soc Am (Nov 18-21, Philadelphia) 1999, Abst 34.
6. Finn, A. et al. *Memory mucosal antibody responses to a pneumococcal conjugate vaccine in infants.* 37th Annu Meet Infect Dis Soc Am (Nov 18-21, Philadelphia) 1999, Abst 645.
7. Klein, J.O. *Management of otitis media: 2000 and beyond.* *Pediatr Infect Dis J* 2000, 19(4): 383.
8. Rennels, M.B. et al. *Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants.* *Pediatrics* 1998, 101(4): 604.
9. Shinefield, H.R. et al. *Safety and immunogenicity of heptavalent pneumococcal CRM197 conjugate vaccine in infants and toddlers.* *Pediatr Infect Dis J* 1999, 18(9): 757.
10. Sorensen, R.U. et al. *Response to a heptavalent conjugate Streptococcus pneumoniae vaccine in children with recurrent infections who are unresponsive to the polysaccharide vaccine.* *Pediatr Infect Dis J* 1998, 17(8): 685.
11. Steele, R.W. *Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants.* *Clin Pediatr* 1998, 37(12): 760.
12. Vernacchio, L. et al. *Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell disease.* *J Pediatr* 1998, 133(2): 275.
13. *Advisory committee supports approval of Prevnar.* *DailyDrugNews.com* (Daily Essentials) 1999, Nov 9.
14. *AHP announces first launch of Prevnar.* *DailyDrugNews.com* (Daily Essentials) 2000, April 4.
15. *AHP's pneumococcal conjugate vaccine receives priority review status.* *DailyDrugNews.com* (Daily Essentials) 1999, July 27.
16. *Another major milestone announced for Wyeth Lederle Vaccines' pneumococcal vaccine.* *DailyDrugNews.com* (Daily Essentials) 1999, Oct 22.
17. *CDC advisory committee recommends Wyeth-Lederle's pneumococcal conjugate vaccine for routine use.* *DailyDrugNews.com* (Daily Essentials) 1999, Oct 27.
18. *FDA approves first vaccine for prevention of invasive pneumococcal disease in infants and toddlers.* *DailyDrugNews.com* (Daily Essentials) 2000, Feb 18.
19. *FDA grants fast track designation for pneumococcal conjugate vaccine.* *DailyDrugNews.com* (Daily Essentials) 1999, March 12.
20. *Vaccine against pneumococcal disease shown safe and immunogenic in children.* *DailyDrugNews.com* (Daily Essentials) 1998, April 14.

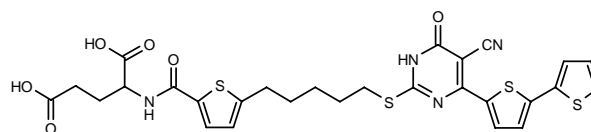
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ONCOLYTIC DRUGS

ANTIMETABOLITES

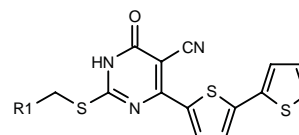
287275

N-[5-[5-[5-Cyano-4-[5-(2-thienyl)-2-thienyl]-6-oxo-1,6-dihydro-2-pyrimidinylsulfanyl]pentyl]-2-thienylcarbonyl]-DL-glutamic acid



C28 H26 N4 O6 S4; Mol wt: 642.7994

ACTION – An inhibitor of the enzyme phosphoribosylaminoimidazolecarboxamide formyltransferase (AICARFT; $K_i = 0.004 \mu\text{M}$) with potential as an antitumor agent, as well as an antiinflammatory, antipsoriatic and immunosuppressive agent. Other compounds from this series of dihydropyrimidone derivatives include the following:



Compound	R1	Formula
287276	5-CO2H-2-thienyl-(CH2)4	C ₂₃ H ₁₉ N ₃ O ₃ S ₄
287277	2-Cl-4-(4-F-PhSO2NH)-Ph	C ₂₆ H ₁₆ ClFN ₄ O ₃ S ₄
287278	4-(3-indolyl-CH2CH2NHSO2)-Ph	C ₃₀ H ₂₃ N ₅ O ₃ S ₄

SOURCE – Agouron (Warner-Lambert [Pfizer]).

REFERENCES

1. Bleckman, T.M. et al. (Agouron Pharmaceuticals, Inc.) *Cpds. useful as AICARFT inhibitors.* WO 0013688.

PRESENTATION – Vials, suspension for i.m. injection, 0.5 ml formulated to contain 2 µg of each saccharide for serotypes 4, 9V, 14, 18C, 19F and 23F, and 4 µg of 6B per dose (16 µg total saccharides), approximately 20 µg of CRM197 carrier protein and 0.125 mg aluminum as aluminum phosphate adjuvant.

PROPRIETARY NAME – *Prevnar* (US).

SOURCE – Wyeth-Ayerst.

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9. Shinefield, H.R. et al. *Safety and immunogenicity of heptavalent pneumococcal CRM197 conjugate vaccine in infants and toddlers.* *Pediatr Infect Dis J* 1999, 18(9): 757.
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17. *CDC advisory committee recommends Wyeth-Lederle's pneumococcal conjugate vaccine for routine use.* *DailyDrugNews.com* (Daily Essentials) 1999, Oct 27.
18. *FDA approves first vaccine for prevention of invasive pneumococcal disease in infants and toddlers.* *DailyDrugNews.com* (Daily Essentials) 2000, Feb 18.
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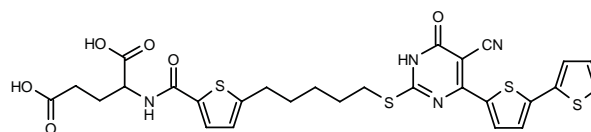
*Drug Data Report 1998, 020(06): 0535.

ONCOLYTIC DRUGS

ANTIMETABOLITES

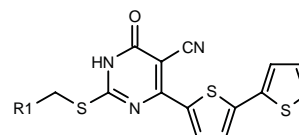
287275

N-[5-[5-[5-Cyano-4-[5-(2-thienyl)-2-thienyl]-6-oxo-1,6-dihydro-2-pyrimidinylsulfanyl]pentyl]-2-thienylcarbonyl]-DL-glutamic acid



C28 H26 N4 O6 S4; Mol wt: 642.7994

ACTION – An inhibitor of the enzyme phosphoribosylaminoimidazolecarboxamide formyltransferase (AICARFT; $K_i = 0.004 \mu\text{M}$) with potential as an antitumor agent, as well as an antiinflammatory, antipsoriatic and immunosuppressive agent. Other compounds from this series of dihydropyrimidone derivatives include the following:



Compound	R1	Formula
287276	5-CO2H-2-thienyl-(CH2)4	C ₂₃ H ₁₉ N ₃ O ₃ S ₄
287277	2-Cl-4-(4-F-PhSO2NH)-Ph	C ₂₆ H ₁₆ ClFN ₄ O ₃ S ₄
287278	4-(3-indolyl-CH2CH2NHSO2)-Ph	C ₃₀ H ₂₃ N ₅ O ₃ S ₄

SOURCE – Agouron (Warner-Lambert [Pfizer]).

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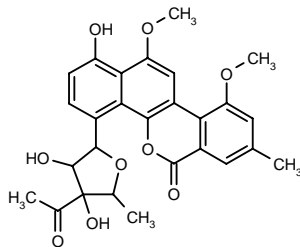
1. Bleckman, T.M. et al. (Agouron Pharmaceuticals, Inc.) *Cpds. useful as AICARFT inhibitors.* WO 0013688.

ANTIBIOTICS AND ALKALOIDS

Mer-1020dA

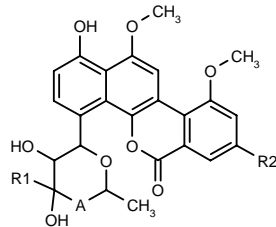
286551

4-(4-Acetyl-3,4-dihydroxy-5-methyltetrahydrofuran-2-yl)-1-hydroxy-8-methyl-10,12-dimethoxy-6*H*-benzo[*d*]-naphtho[1,2-*b*]pyran-6-one



C27 H26 O9; Mol wt: 494.4934

ACTION – Antitumor antibiotic, a representative compound from a series of *C*-glycosides produced by *Streptomyces* sp. Mer-1020 (FERM P-15888) with superior growth-inhibitory activity against solid tumor cells compared to the structurally related chrysomycins, and low toxicity. *In vitro*, compound exhibited potent cytotoxicity against human leukemia K562, colon cancer HT-29, breast cancer MCF-7, lung cancer PC-6 and gastric cancer MKN28 cell lines, with IC₅₀ values of 0.36, 0.075, 0.032, 0.064 and 0.017 µg/ml, respectively, vs. IC₅₀ values of 0.106, 0.84, 0.53, 0.335 and 0.144 µg/ml, respectively, for chrysomycin A and of 1.76, 2.63, 2.58, 3.5 and 2.65 µg/ml, respectively, for chrysomycin B. Other compounds isolated from the same source are:



Compound	R1	R2	A	Formula
Mer-1020dB [286552]	Me	Me	-CO-	C ₂₇ H ₂₆ O ₉
Mer-1020dC [286553]	Me	vinyl	-CO-	C ₂₈ H ₂₆ O ₉
Mer-1020dD [286554]	Ac	vinyl	bond	C ₂₈ H ₂₆ O ₉

SOURCE – Mercian.

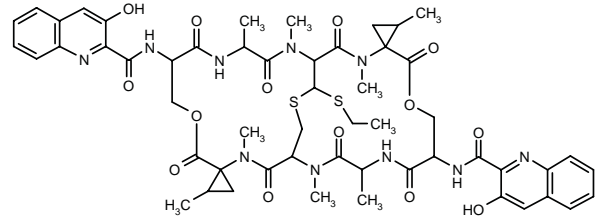
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SW-163E

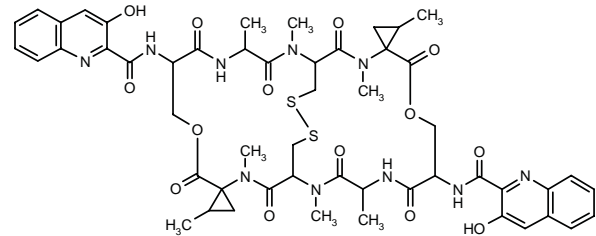
287341

27'-(Ethylsulfanyl)-7',20'-bis(3-hydroxyquinolin-2-ylcarboxamido)-2,2',2'',4',12',15',17',25'-octamethyl-dispiro[cyclopropane-1,11'-9',22'-dioxo-28'-thia-2',5',12',15',18',25'-hexaazabicyclo[12.12.3]nonacosane-24',1''-cyclopropane]-3',6',10',13',16',19',23',26'-octaone



C54 H64 N10 O14 S2; Mol wt: 1141.2880

ACTION – Antineoplastic agent produced by *Streptomyces* sp. SNA 15896 (FERM BP-6735) with potent cytotoxicity against murine leukemia P388, vincristine-resistant P388/VCR, murine colon cancer 26, human ovarian cancer A2780, the multidrug-resistant A2780 subline AD10, human leukemia HL-60 and human nasopharyngeal cancer KB cells (IC₅₀ = 0.3, 2.0, 1.6, 0.2, 50, 1.3 and 0.4 nM, respectively). *In vivo*, compound increased survival in mice bearing P388 leukemia (T/C = 142% at 10 µg/kg i.p. on days 1 and 5), P388/VCR leukemia (T/C = 143% at 30 µg/kg i.p. on days 1 and 5) and B16 melanoma (T/C = 174% at 10 µg/kg/day i.p. x 9 days). Compound also exhibits some activity against certain bacteria. Another compound isolated from the same source is:



SW-163C [287342]: C52 H60 N10 O14 S2

SOURCE – Snow Brand.

REFERENCES

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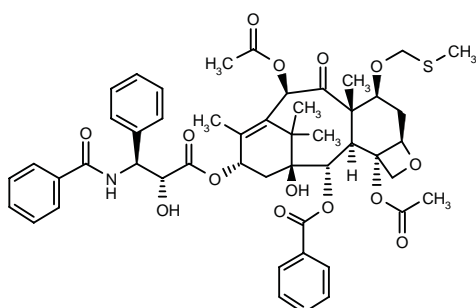
ANTIMITOTIC DRUGS

BMS-184476

275943

7-*O*-(Methylsulfonylmethyl)paclitaxel

3(*S*)-Benzamido-2(*R*)-hydroxybenzenepropionic acid (2*aR*,4*S*,4*aS*,6*R*,9*S*,11*S*,12*S*,12*aR*,12*bS*)-6,12*b*-diacetoxy-12-(benzoyloxy)-11-hydroxy-4*a*,8,12,13-tetramethyl-4-(methylsulfonylmethoxy)-5-oxo-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-9-yl ester



C49 H55 N O14 S; Mol wt: 914.0325

ACTION – Antineoplastic agent, a taxane analogue with increased *in vivo* efficacy compared to paclitaxel. Compound showed similar cytotoxic effects to paclitaxel against 23 cell lines which did not contain mutated tubulin or high levels of multidrug resistance (MDR) including ovarian carcinoma A2780 cells (IC_{50} = 2.3 and 2.2 nM, for compound and paclitaxel, respectively) and colon carcinoma HCT 116 cells (IC_{50} = 2.1 and 2.2 nM, respectively); however, it was more active than paclitaxel against A2780 cells expressing mutated tubulin (IC_{50} = 17.9 and 76.3 nM, respectively), as well as against HCT 116 expressing high levels of MDR (IC_{50} = 28.7 and > 117 nM, respectively). Both compounds induce arrest in the G2/M phase of the cell cycle and apoptosis both in wild-type and mutant human ovarian carcinoma A2780 cells. In addition, title compound was shown to enhance the effects of radiation in human lung cancer H460 cells. Ongoing phase I trials in patients with solid tumors have indicated that compound has a more favorable toxicity profile than paclitaxel; neutropenia and diarrhea were dose-limiting when compound was given by 1-h infusion weekly every 3 weeks in combination with carboplatin.

SOURCE – Bristol-Myers Squibb.

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- Hidalgo, M. et al. A phase I and pharmacokinetic (PK) study of the taxane analog, BMS 184476, administered as a 1-hour IV infusion every 3 weeks. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 332.

5. Hidalgo, M. et al. Phase I and pharmacokinetics (PK) study of BMS 184476, a potent and soluble taxane analog, as a 1-hour infusion every 3 weeks. Proc Am Soc Clin Oncol 1999, 18: Abst 645.

6. Highley, M. et al. Phase I and pharmacokinetics (PK) study of BMS-184476, a new taxane analog, given weekly in patients with advanced malignancies. Proc Am Soc Clin Oncol 1999, 18: Abst 644.

7. Kadow, J.F. et al. Discovery of more efficacious analogs of paclitaxel (Taxol) for human clinical evaluation. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 298.

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9. Sessa, C. et al. Phase I study of BMS-184476, a new taxane analog, given weekly in patients with advanced malignancies. Eur J Cancer 1999, 35(Suppl. 4): Abst 1142.

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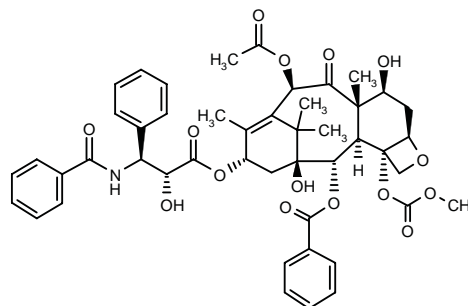
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BMS-188797

282724

4-*O*-Deacetyl-4-*O*-(methoxycarbonyl)paclitaxel

3(*S*)-Benzamido-2(*R*)-hydroxybenzenepropionic acid (2*aR*,4*S*,4*aS*,6*R*,9*S*,11*S*,12*S*,12*aR*,12*bS*)-6-acetoxy-12-(benzoyloxy)-4,11-dihydroxy-12*b*-(methoxycarbonyloxy)-4*a*,8,13,13-tetramethyl-5-oxo-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-9-yl ester



C47 H51 N O15; Mol wt: 869.9119

ACTION – Antineoplastic agent, a taxane analogue with higher potency and a wider spectrum of preclinical activity than paclitaxel. Compound was more active than paclitaxel against irradiated human lung carcinoma H460 cells (IC_{50} = 58 and 410 nM, respectively), and was shown to enhance the effects of radiation *in vitro* against human lung cancer cells and to block the cell cycle in the G2/M phase. *In vivo*, compound demonstrated superior activity compared to paclitaxel in murine tumor models including murine lung carcinoma M109 and both the moderately paclitaxel-resistant human colon carcinoma HCT/pk and human ovarian carcinoma HOC79 xenografts. Tissue pharma-cokinetic studies in mice demonstrated sustained tumor uptake of compound relative to the plasma half-life. Preliminary phase I clinical studies in patients with advanced cancer indicated that compound (administered every 21 days as a 1-h infusion at a starting dose of 3.75 mg/m²) possesses pharmacokinetics similar to paclitaxel, with a half-life of 27 h, clearance of 156 ml/min/m² and volume of distribution of 198 l/m². No hypersensitivity reactions to the drug formulated in Cremaphor were reported.

SOURCE – Bristol-Myers Squibb.

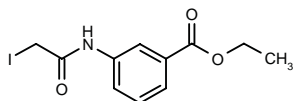
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3-IAABE

287230

3-(2-Iodoacetamido)benzoic acid ethyl ester



C11 H12 I N O3; Mol wt: 333.1198

ACTION – Antineoplastic agent, an inhibitor of microtubule assembly that binds at the colchicine site of β -tubulin and induces cell cycle arrest at the G1/S transition and in the M phase; it also induces apoptosis. Compound showed antitumor activity against 62 human tumor cells lines, with IC_{50} values of 0.289-3.25 μ M for solid tumors, and 0.048-1.18 μ M for leukemias. In mice bearing prostate tumor cells, compound given at a dose of 25 mg/kg for 7 days exhibited equivalent tumor inhibition compared with paclitaxel (tumor growth inhibition = 85 and 80%, respectively). Compound was seen to induce complete remission in 20% of animals after 90-day repeated treatment, whereas no complete tumor remission was seen in animals treated with paclitaxel under the same conditions.

SOURCES – Cytoskeleton; Mount Sinai School of Medicine, New York, NY (US); Texas Biotechnology.

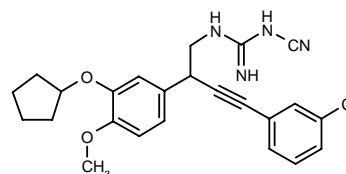
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HORMONAL AGENTS

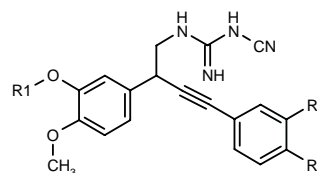
286634

(\pm)-*N*¹-[4-(3-Chlorophenyl)-2-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-butyryl]-*N*³-cyanoguanidine



C24 H25 Cl N4 O2; Mol wt: 436.9405

ACTION – Nonpeptide gastrin-releasing peptide (GRP) receptor antagonist with potential in the treatment of chronic renal failure and prostate cancer, as well as small cell and non-small cell lung carcinoma, breast cancer, gastric carcinoma, glioblastoma, colon cancer, thyroid cancer and pituitary tumors. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
286635	cyclopentyl	H	Cl	C ₂₄ H ₂₅ ClN ₄ O ₂
286636	cyclopentyl	Cl	F	C ₂₄ H ₂₄ ClFN ₄ O ₂
286637	cyclopentyl	F	Cl	C ₂₄ H ₂₄ ClFN ₄ O ₂
286638	cyclopentyl	F	F	C ₂₄ H ₂₄ F ₂ N ₄ O ₂
286639	cyclopentyl	OMe	H	C ₂₅ H ₂₈ N ₄ O ₃
286640	cyclopentyl	H	OCF ₃	C ₂₅ H ₂₅ F ₃ N ₄ O ₃
286641	cyclopentyl	CF ₃	H	C ₂₅ H ₂₅ F ₃ N ₄ O ₂
286642	C ₁₀ H ₂₁	H	H	C ₂₉ H ₃₈ N ₄ O ₂

SOURCE – SmithKline Beecham.

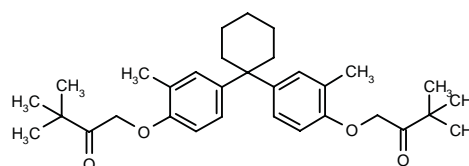
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286719

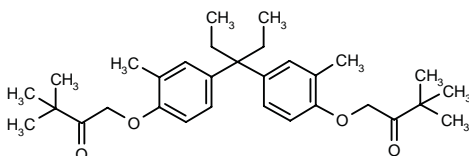
1,1-Bis[4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl]-cyclohexane

1,1'-(Cyclohexylidene)bis(2-methyl-4,1-phenylene)-bisoxobis(3,3-dimethyl-2-butanone)



C32 H44 O4; Mol wt: 492.6956

ACTION – Vitamin D₃ mimic that modulates the vitamin D₃ receptor (VDR), found to elicit VDR-dependent transcription in a cotransfection assay, while showing no binding affinity for the serum vitamin D-binding protein (DBP), indicating that it may have a reduced potential for undesirable calcium mobilization effects. The compound inhibited cancer cell and keratinocyte growth and induced monocyte differentiation of HL-60 leukemia cells *in vitro*. *In vivo* results demonstrated antitumor activity in a nude mouse prostate cancer model and no hypercalcemia. Potentially useful, particularly in combination with retinoids and more particularly with RXR (retinoid X receptor)-selective retinoids (rexinoids), or androgen receptor modulators, for the treatment of cancer, particularly prostate cancer, and for treating psoriasis, osteoporosis, rheumatoid arthritis, Alzheimer's disease, autoimmune diseases, etc. Another related compound is:



286721: C31 H44 O4

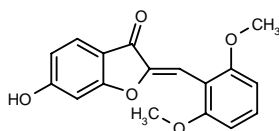
SOURCE – Ligand.

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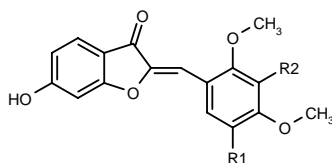
286844

2-[(Z)-2,6-Dimethoxybenzylidene]-6-hydroxy-2,3-dihydro-1-benzofuran-3-one



C17 H14 O5; Mol wt: 298.2926

ACTION – Agent for the treatment of hormone-dependent disorders that acts by inhibiting 17 β -hydroxysteroid dehydrogenase (17 β -HSD). Other compounds from this series of benzofuranone derivatives include the following:



Compound	R1	R2	Formula
286845	OMe	H	C ₁₈ H ₁₆ O ₆
286846	H	OMe	C ₁₈ H ₁₆ O ₆

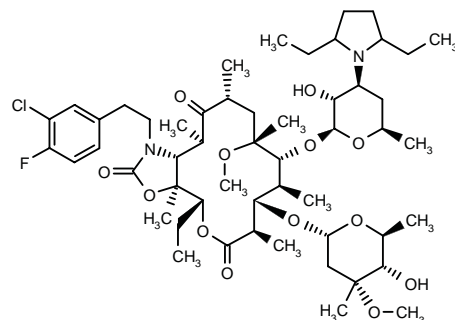
SOURCE – Snow Brand.

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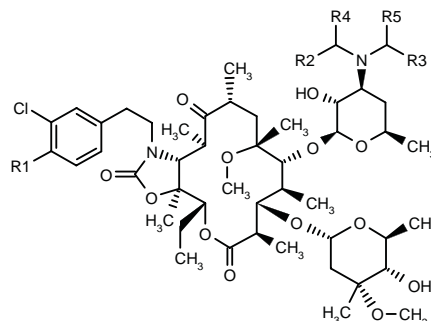
287102

11-[2-(3-Chloro-4-fluorophenyl)ethylamino]-11-deoxy-3'-des(dimethylamino)-3'-(2,5-diethylpyrrolidin-1-yl)-6-O-methylerythromycin A 11-N,12-O-cyclic carbamate



C53 H84 Cl F N2 O13; Mol wt: 1011.6990

ACTION – LHRH (luteinizing hormone-releasing hormone, or gonadotropin-releasing hormone) antagonist with a pK_i value for binding to rat pituitary LHRH receptors of 9.17. It is therefore expected to be useful in the treatment of precocious puberty, prostate cancer, benign prostatic hyperplasia (BPH), endometriosis, uterine fibroids, breast cancer, acne, premenstrual syndrome, polycystic ovary syndrome, as well as for controlling reproduction in both males and females. Other exemplified compounds from this series of 3',3'-N-bis-desmethyl-3'-N-cycloalkyl erythromycin derivatives are:



Compound	R1	R2=R3	R4,R5	Formula
287108	Cl	H	-(CH2)2-	C ₄₉ H ₇₆ Cl ₂ N ₂ O ₁₃
287109	Cl	H	-(CH2)3-	C ₅₀ H ₇₈ Cl ₂ N ₂ O ₁₃
287110	F	H	-(CH2)3-	C ₅₀ H ₇₈ ClFN ₂ O ₁₃
287111	Cl	Me	-(CH2)2-	C ₅₁ H ₈₀ Cl ₂ N ₂ O ₁₃
287112	F	Me	-(CH2)2-	C ₅₁ H ₈₀ ClFN ₂ O ₁₃
287113	Cl	Me	-(CH2)3-	C ₅₂ H ₈₂ Cl ₂ N ₂ O ₁₃
287114	F	Me	-(CH2)3-	C ₅₂ H ₈₂ ClFN ₂ O ₁₃
287115	Cl	Et	-(CH2)2-	C ₅₃ H ₈₄ Cl ₂ N ₂ O ₁₃
287116	F	cyclopropyl	-(CH2)3-	C ₅₆ H ₈₆ ClFN ₂ O ₁₃

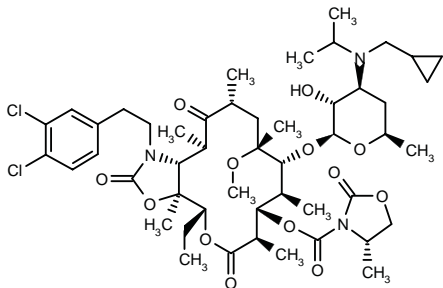
SOURCE – Abbott.

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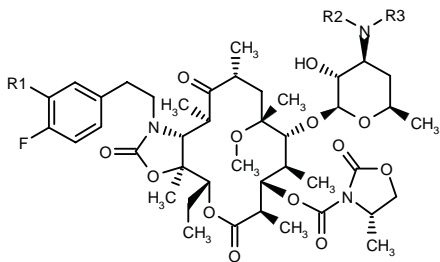
287159

3'-*N*-Cyclopropylmethyl-11-deoxy-3-*O*-des(hexopyranosyl)-3'-*N,N*-bis(desmethyl)-11-[2-(3,4-dichlorophenyl)ethylamino]-3'-*N*-isopropyl-3-*O*-[4(*S*)-methyl-2-oxooxazolidin-3-ylcarbonyl]-6-*O*-methylerythromycin A 11-*N*,12-*O*-cyclic carbamate



C49 H73 Cl2 N3 O13; Mol wt: 983.0297

ACTION – LHRH (luteinizing hormone-releasing hormone, or gonadotropin-releasing hormone) antagonist, as demonstrated in *in vitro* tests using rat pituitary cells ($pK_i = 10.13$). Potentially useful for the treatment of precocious puberty, prostate cancer, breast cancer, benign prostatic hyperplasia (BPH), endometriosis, uterine fibroids, acne, premenstrual syndrome, polycystic ovary syndrome, as well as for controlling reproduction in both females and males. Other exemplified 3'-*N*-desmethyl-3'-*N*-substituted-6-*O*-methyl-11,12-cyclic carbamate erythroside A derivatives include the following:



Compound	R1	R2	R3	Formula
287160	H	cyclobutyl	Me	C ₄₇ H ₇₀ FN ₃ O ₁₃
287161	H	cyclopentyl	Me	C ₄₈ H ₇₂ FN ₃ O ₁₃
287162	H	i-Pr	Me	C ₄₆ H ₇₀ FN ₃ O ₁₃
287163	Cl	cyclopropyl-CH2	Me	C ₄₇ H ₆₉ ClFN ₃ O ₁₃
287164	Cl	cyclobutyl	Me	C ₄₇ H ₆₉ ClFN ₃ O ₁₃
287165	Cl	cyclopropyl-CH2	i-Pr	C ₄₉ H ₇₃ ClFN ₃ O ₁₃

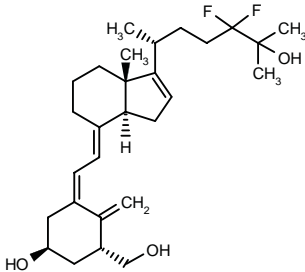
SOURCE – Abbott.

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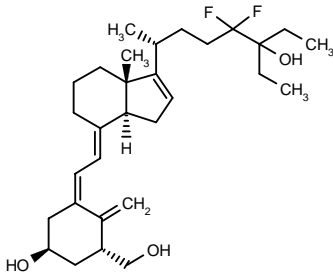
287531

(+)-(1 β ,3 α)-24,24-Difluoro-25-hydroxy-1-(hydroxymethyl)-16,17-didehydrovitamin D₃



C28 H42 F2 O3; Mol wt: 464.6328

ACTION – Fluorinated analogue of 1 α ,25-dihydroxyvitamin D₃ with comparable antiproliferative activity, as demonstrated *in vitro* in murine keratinocytes and B16 melanoma cells, and transcriptional activity ($ED_{50} = 0.2$ nM vs. 0.3 nM for calcitriol in rat osteosarcoma ROS 17/2.8 cells), and little or no calcemic activity, as demonstrated *in vivo* in rats following oral administration. Another exemplified compound is:



287532: C30 H46 F2 O3

SOURCE – Johns Hopkins University, Baltimore, MD (US).

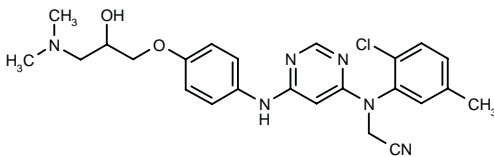
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INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

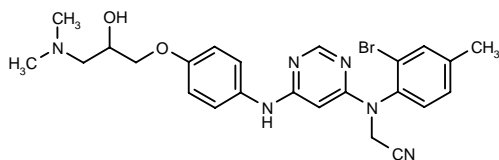
286964

2-[*N*-(2-Chloro-5-methylphenyl)-*N*-[6-[4-[3-(dimethylamino)-2-hydroxypropoxy]phenylamino]-pyrimidin-4-yl]amino]acetonitrile



C24 H27 Cl N6 O2; Mol wt: 466.9703

ACTION – An inhibitor of cyclin-dependent kinases, particularly cdk2, cdk4 and cdk6, potentially useful in the treatment of disease states associated with aberrant cell cycles and cell proliferation, such as cancer. *In vitro*, compound exhibited an IC_{50} value of 0.07 μ M for inhibition of cdk4. Another compound from this series of pyrimidine derivatives is:



286965: C₂₄ H₂₇ Br N₆ O₂

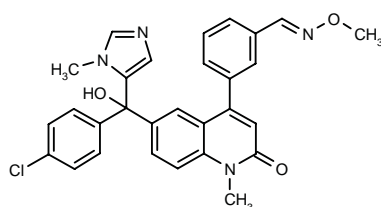
SOURCE – AstraZeneca.

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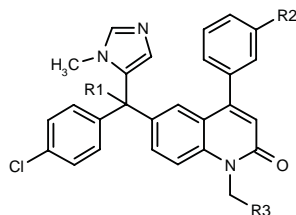
287024

3-[6-[1-(4-Chlorophenyl)-1-hydroxy-1-(1-methyl-1H-imidazol-5-yl)methyl]-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl]benzaldehyde *O*-methyloxime



C₂₉ H₂₅ Cl N₄ O₃; Mol wt: 512.9945

ACTION – Antineoplastic agent with protein farnesyl-transferase-inhibitory activity. Other specifically claimed compounds from this series of quinolin-2-one derivatives include the following:



Compound	R1	R2	R3	Formula
287025	OH	CH=NOEt	H	C ₃₀ H ₂₇ ClN ₄ O ₃
287026	OH	Cl	cyclopropyl	C ₃₀ H ₂₅ Cl ₂ N ₃ O ₂
287027	NH ₂	Cl	cyclopropyl	C ₃₀ H ₂₆ Cl ₂ N ₄ O
287028	1,2,4-triazol-1-yl	Cl	cyclopropyl	C ₃₂ H ₂₆ Cl ₂ N ₆ O

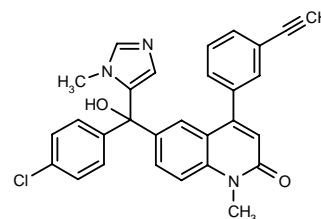
SOURCE – Pfizer.

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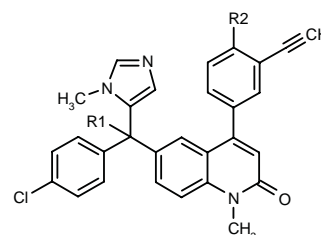
287041

6-[1-(4-Chlorophenyl)-1-hydroxy-1-(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethynylphenyl)-1-methylquinolin-2(1H)-one enantiomer A



C₂₉ H₂₂ Cl N₃ O₂; Mol wt: 479.9648

ACTION – Antineoplastic agent with protein farnesyl-transferase-inhibitory activity. Other specifically claimed compounds from this series of alkynyl-substituted quinolin-2-one derivatives include the following:



Compound	R1	R2	Isomer	Formula
287042	OH	H	B	C ₂₉ H ₂₂ ClN ₃ O ₂
287043	NH ₂	H	A	C ₂₉ H ₂₃ ClN ₄ O
287044	NH ₂	H	B	C ₂₉ H ₂₃ ClN ₄ O
287045	OH	F		C ₂₉ H ₂₁ ClFN ₃ O ₂

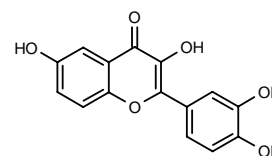
SOURCE – Pfizer.

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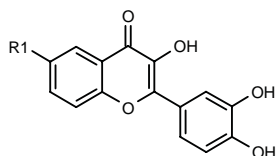
287046

2-(3,4-Dihydroxyphenyl)-3,6-dihydroxy-4H-1-benzopyran-4-one



C₁₅ H₁₀ O₆; Mol wt: 286.2380

ACTION – Antineoplastic agent, an inhibitor of cyclin-dependent kinases with IC_{50} values of < 5 μ M against cdk2 and cdk4 kinases. LD_{50} > 3000 mg/kg p.o in mice. Compound is reported to possibly also inhibit cdk5, which may render it useful for the treatment of neuro-degenerative diseases. Other compounds from this series of flavone derivatives include the following:



Compound	R1	Formula
287047	F	C ₁₅ H ₉ FO ₅
287048	4-Me-PhSO ₂ NH	C ₂₂ H ₁₇ NO ₇ S
287049	4-CF ₃ -PhSO ₂ NH	C ₂₂ H ₁₄ F ₃ NO ₇ S
287050	NHAc	C ₁₇ H ₁₃ NO ₆
287051	NHCONHCOPh	C ₂₃ H ₁₆ N ₂ O ₇

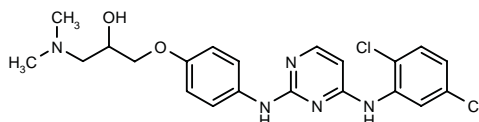
SOURCE – LG Chem.

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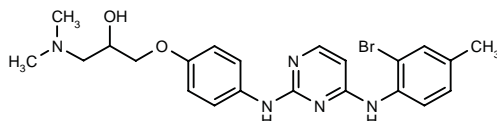
287131

1-[4-[4-(2,5-Dichlorophenylamino)pyrimidin-2-ylamino]-phenoxy]-3-(dimethylamino)propan-2-ol



C₂₁ H₂₃ Cl₂ N₅ O₂; Mol wt: 448.3517

ACTION – Cell cycle kinase inhibitor with selectivity for cdk2, cdk4 and cdk6, and also FAK (focal adhesion kinase), with IC₅₀ values in *in vitro* assays evaluating cdk4- and FAK-inhibitory activity of 0.53 and 3.1 μM, respectively. It is expected to be useful as an anticancer agent with antiproliferative, antimigration and/or apoptotic properties, as well as other disease states associated with aberrant cell cycles and cell proliferation, i.e., psoriasis, rheumatoid arthritis, hemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases associated with retinal vessel proliferation. Another exemplified pyrimidine derivative is:



287134: C₂₂ H₂₆ Br N₅ O₂

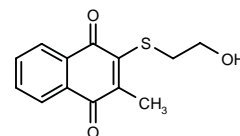
SOURCE – AstraZeneca.

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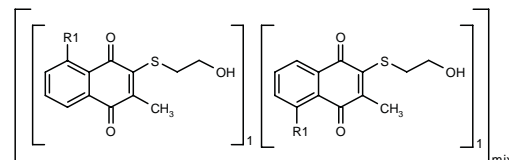
287241¹⁻¹²

2-(2-Hydroxyethylsulfanyl)-3-methylnaphthoquinone



C₁₃ H₁₂ O₃ S; Mol wt: 248.3008

ACTION – Antineoplastic agent, a synthetic vitamin K analogue proven to strongly inhibit the growth of a panel of tumor cell lines including liver Hep3B cells (IC₅₀ = 5.6 μM), pancreatic PANC-1 cells (IC₅₀ = 31.8 μM), doxorubicin-sensitive and -resistant breast cancer MCF-7 cells (IC₅₀ = 10 μM), and estrogen-sensitive and -resistant breast cancer SK-BR-3 and MDA-MB-231 cells (IC₅₀ = 10 μM). Compound was also shown to induce selective phosphorylation of several cellular proteins including epidermal growth factor (EGF) receptor tyrosine kinase and extracellular regulated kinase (ERK), and to inhibit human recombinant Cdc25B (IC₅₀ = 3.8 μM). In an *in vivo* model of liver cell regeneration following partial hepatectomy in rats, compound delayed hepatocyte DNA synthesis by 48 h and inhibited ERK-specific phosphatase. Other related compounds include the following:



Compound	R1	Mixture	Formula
287437^{1,2}	NHAc	1:1	C ₁₅ H ₁₅ NO ₄ S
287438^{1,2}	NO ₂	1:1	C ₁₃ H ₁₁ NO ₅ S

SOURCE – University of Pittsburgh, Pittsburgh, PA (US).

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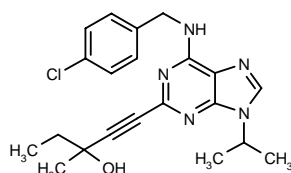
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287500

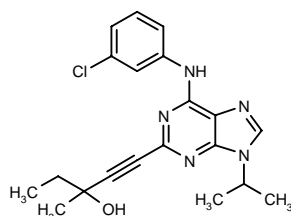
1-[6-(4-Chlorobenzylamino)-9-isopropyl-9H-purin-2-yl]-3-methyl-1-pentyn-3-ol



C21 H24 Cl N5 O; Mol wt: 397.9076

M.p. 138-42 °C.

ACTION – Potent inhibitor of the cyclin-dependent kinase cdk1/cyclin B (IC_{50} = 60 nM) with 4-fold lower activity against cdk5/p35. Potentially useful for molecular modeling studies to design more potent and selective cyclin-dependent kinase inhibitors. Within this series of acetylenic purines, the following is also included:



287501: C20 H22 Cl N5 O

SOURCE – CNRS.

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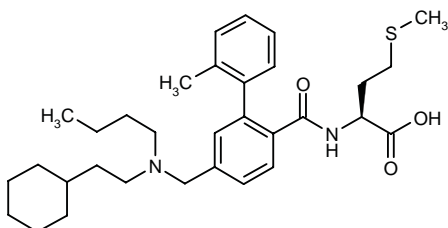
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A-228839

287069

N-[5-[*N*-Butyl-*N*-(2-cyclohexylethyl)aminomethyl]-2'-methylbiphenyl-2-ylcarbonyl]-L-methionine

A-228839.25 (as sulfate)



C32 H46 N2 O3 S; Mol wt: 538.7924

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase.

SOURCES – Abbott; University of Pittsburgh, Pittsburgh, PA (US).

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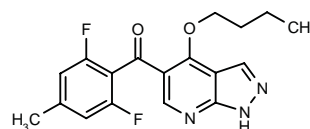
BMS-265246

286967

1-(4-Butoxy-1H-pyrazolo[3,4-b]pyridin-5-yl)-1-(2,6-difluoro-4-methylphenyl)methanone

4-Butoxy-5-(2,6-difluoro-4-methylbenzoyl)-1H-pyrazolo[3,4-b]pyridine

BMS-265246-01



C18 H17 F2 N3 O2; Mol wt: 345.3473

ACTION – Potent ATP-competitive inhibitor of the cyclin-dependent kinase cdk2/cyclin E (IC_{50} = 9 nM) with more than 200-fold selectivity over cdk4/cyclin D kinase (IC_{50} = 230 nM). Compound showed cytotoxic activity against human ovarian cancer A2780 cells (CC_{50} = 760 nM). Potentially useful as an antineoplastic agent for use alone or in combination with other existing therapies.

SOURCE – Bristol-Myers Squibb.

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CETUXIMAB

Prop INN; USAN

230562

Immunoglobulin G₁ (human-mouse monoclonal C225 γ 1-chain anti-human epidermal growth factor receptor), disulfide with human-mouse monoclonal C225 κ -chain dimer

IMC-C225

C225

ACTION – Antineoplastic agent, a chimeric monoclonal antibody directed against epidermal growth factor (EGF) receptor proven to exert cytostatic effects in tumor cells overexpressing the EGF receptor, as well as radiosensitizing and chemosensitizing effects. Compound showed strong *in vitro* cytotoxic activity against pancreatic carcinoma xenografts doses of 17 and 33 mg/kg significantly inhibited growth of established tumors. Moreover, preclinical experiments showed that combination therapy with paclitaxel enhanced the apoptotic and antiangiogenic effects of the compound alone, and compound greatly increased tumor response to local tumor irradiation. Phase I clinical studies showed good safety, dose-dependent pharmacokinetics and receptor-blocking serum levels with a weekly administration schedule. Several phase II and III clinical studies are under way to evaluate the compound in combination with radiotherapy or chemotherapy for the treatment of solid tumors.

SOURCES – ImClone Systems; Merck KGaA.

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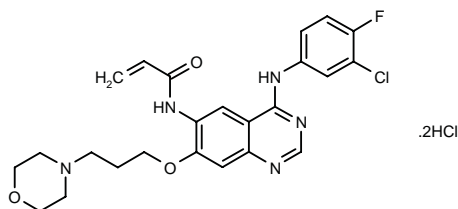
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CI-1033

274534

N-[4-(3-Chloro-4-fluorophenylamino)-7-[3-(4-morpholinyl)-propoxy]quinazolin-6-yl]-2-propenamide dihydrochloride

PD-183805 (free base)



C24 H25 Cl F N5 O3 . 2HCl; Mol wt: 558.8663

M.p. 188-90 °C.

ACTION – Antineoplastic agent, a potent and irreversible epidermal growth factor (EGF) receptor tyrosine kinase inhibitor (IC_{50} = 1.5 and 7.4 nM, respectively, for inhibition of EGF receptor phosphorylation and EGF-stimulated EGF receptor autophosphorylation in human epidermoid carcinoma A-431 cells); it binds and inactivates the erbB2 gene and inhibits heregulin-stimulated autophosphorylation of erbB2 in human breast carcinoma MDA-MB-453 cells (ID_{50} = 9 nM). Compound was shown to block the growth and invasion of human breast cancer cells

overexpressing the erbB2 gene and to strongly enhance radiation-induced cell killing. *In vivo*, it was capable of suppressing EGF receptor tyrosine phosphorylation by more than 80% for 72 h after administration (2.5-40 mg/kg p.o. 1, 2, 3 or 5 times per week for 3 weeks) and it was able to delay the growth of A-431 xenografts in mice after oral treatment at the optimal dose of 5 mg/kg/day; maximal growth delay in these studies was approximately 50 days, and the therapeutic index was consistently greater than 8. Selected for clinical evaluation.

SOURCE – Warner-Lambert (Pfizer).

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10. Smaill, J.B. et al. Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(Phenylamino)quinazoline- and 4-(phenylamino)-pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions. J Med Chem 2000, 43(7): 1380.

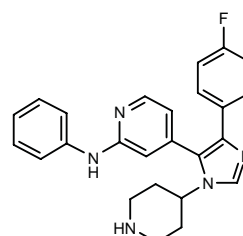
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12. Woods Ignatoski, K.M. et al. A small molecule, erbB kinase inhibitor blocks growth and invasion of human breast cancer cells and sensitizes them to ionizing radiation. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 365.

SB-238039

287190

N-[4-[4-(4-Fluorophenyl)-1-(4-piperidinyl)-1H-imidazol-5-yl]pyridin-2-yl]-N-phenylamine



C25 H24 F N5; Mol wt: 413.4976

ACTION – Antineoplastic agent, an inhibitor of both serine/threonine and tyrosine kinases with IC_{50} values of 7 and 0.05 μ M, respectively, against protein kinase A and C, 3 μ M against CSBP/p38 MAP kinase, and 2.3 and 3 μ M, respectively, against endothelial growth factor (EGF) receptor kinase and Lck tyrosine kinase. Compound showed potent cytotoxic activity against several tumor cell lines *in vitro* ($IC_{50} \sim 2 \mu$ M) and in tumor models *in vivo*. Results from experiments conducted to ascertain its mechanism(s) of action indicated that its antitumor activity may involve inhibition of Jak2 activation or direct inhibition of Jak2.

SOURCE – SmithKline Beecham.

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ANGIOGENESIS INHIBITORS

286216

Recombinant bovine connective tissue growth factor

ACTION – Antiangiogenic polypeptide having an insulin-like growth factor (IGF) binding domain, a von Willebrand factor type C repeat, a thrombospondin type 1 domain and a C-terminal cysteine knot profile, shown to inhibit basic fibroblast growth factor (bFGF)-stimulated proliferation of cultured bovine capillary endothelial cells ($IC_{50} = 50$ -100 ng/ml), being more potent than angiostatin and endostatin. *In vivo* expression of test compound resulted in complete inhibition of the growth of human melanoma implanted s.c. in nude mice.

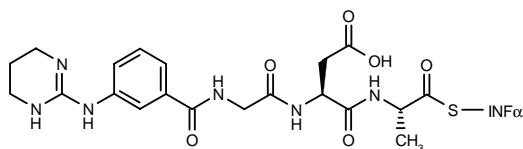
SOURCE – Children's Medical Center Corp.

REFERENCES

1. Folkman, J. and Lin, J. (Children's Medical Center Corp.) *Methods and compsns. for inhibition of angiogenesis.* WO 0005356.

286625

N-[3-(1,4,5,6-Tetrahydropyrimidin-2-ylamino)benzoyl]-glycyl-L-aspartyl-L-alanine thioester conjugate with interferon alfa



ACTION – Conjugate of an $\alpha_v\beta_3$ (vitronectin receptor) antagonist moiety and interferon alfa with potential in the treatment of cancer and other angiogenesis-mediated diseases, particularly arthritis and macular degeneration.

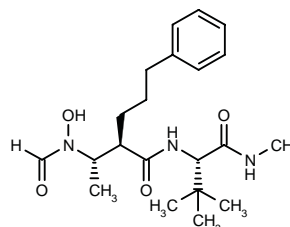
SOURCE – Pharmacia.

REFERENCES

1. Fok, K.F. and Tjoeng, F.S. (G.D. Searle & Co.) *Multivalent $\alpha_v\beta_3$ and metastasis-associated receptor ligands.* WO 0009143.

287117

N-[2,2-Dimethyl-1-(*S*)-(N-methylcarbamoyl)propyl]-2-(*R*)-[1-(*S*)-(N-hydroxyformamido)ethyl]-5-phenylpentanamide



C21 H33 N3 O4; Mol wt: 391.5087

ACTION – Potent, orally active inhibitor of matrix metalloproteinases (MMPs), TNF- α release from monocytes via inhibition of TNF- α -converting enzyme (TACE), shedding of cell-surface protein ectodomains and CD23 proteolysis, with potential for inhibiting the growth of tumor metastases, as well as for treating arthritis and diabetes. *In vitro*, compound gave K_i values of 0.5-5 nM against collagenase 3 and gelatinase B, and of 50-500 nM against TACE, collagenase 1 and stromelysin 1. *In vivo*, compound proved active in tumor-bearing mice, producing 26-50% inhibition of tumor growth in nude mice bearing murine Lewis lung M27 carcinoma and B16B6 melanoma, 51-75% inhibition of human colon adenocarcinoma COLO 205 and SW620 and murine prostate Mat Ly Lu tumors, and complete tumor regression in animals bearing human lung carcinoma A549 at a dose of 30 or 90 mg/kg/day p.o. for 14 days. A representative compound from a series of formamide derivatives.

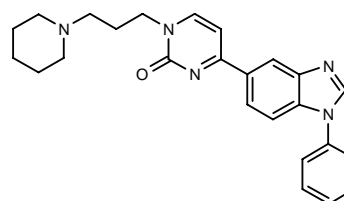
SOURCE – Glaxo Wellcome.

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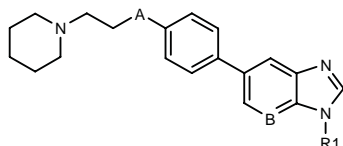
287182

4-(1-Phenyl-1*H*-benzimidazol-5-yl)-1-[3-(1-piperidinyl)propyl]pyrimidin-2(1*H*)-one



C25 H27 N5 O; Mol wt: 413.5223

ACTION – Antiangiogenic agent, an inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinase with selectivity over related tyrosine kinases such as FGFR1 and Src. *In vitro*, compound is reported to inhibit VEGF-stimulated mitogenesis of human umbilical vein endothelial cells (HUVECs) in culture with an IC₅₀ value in the range 150-650 nM. Potentially useful for the treatment or prevention of cancer, ocular diseases such as retinal vascularization, diabetic retinopathy and age-related macular degeneration, and inflammatory diseases such as rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions. Other exemplified



Compound	R1	A	B	Formula
287184	3-thienyl	CH2	N	C ₂₄ H ₂₆ N ₄ S
287187	2-thiazolyl	CH2	N	C ₂₃ H ₂₅ N ₅ S
287188	3-thienyl	CH2	CH	C ₂₅ H ₂₇ N ₃ S
287189	Ph	O	N	C ₂₅ H ₂₆ N ₄ O
287192	2-thiazolyl	CH2	CH	C ₂₄ H ₂₆ N ₄ S

SOURCE – Merck & Co.

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1. Bildeau, M.T. et al. (Merck & Co., Inc.) *Novel angiogenesis inhibitors*. WO 0012089.

JKC-362

287432

Endostatin(54-114)-NH₂ (human)

H-Ala-Asp-Arg-Ala-Ala-Val-Pro-Ile-Val-Asn-Leu-Lys-Asp-Glu-Leu-Leu-Phe-Pro-Ser-Trp-Glu-Ala-Leu-Phe-Ser-Gly-Ser-Glu-Gly-Pro-Leu-Lys-Pro-Gly-Ala-Arg-Ile-Phe-Ser-Phe-Asp-Gly-Lys-Asp-Val-Leu-Arg-His-Pro-Thr-Trp-Pro-Gln-Lys-Ser-Val-Trp-His-Gly-Ser-Asp-Pro-Asn-NH₂

C321 H482 N86 O90; Mol wt: 6985.8510

ACTION – Antineoplastic agent, a water-soluble active fragment of human endostatin with potent antitumor activity *in vivo* but devoid of effects against tumor cells *in vitro*. A putative antiangiogenic agent, compound was shown to inhibit the expansion of human tumor xenografts in nude mice. Another active endostatin fragment is:

Endostatin(84-114)-NH₂ (human)

JKC-367 [287433]: C161 H235 N47 O44

SOURCES – Louisiana State University, Baton Rouge, LA (US); Phoenix Pharmaceuticals.

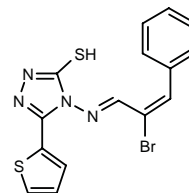
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1. Hunt, J.D. et al. *Internal peptides within endostatin lacking zinc-binding domains inhibit angiogenesis*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3106.

OTHER ONCOLYTIC DRUGS

286765

4-(2-Bromo-3-phenyl-2-propenylideneamino)-5-(2-thienyl)-4*H*-1,2,4-triazole-3-thiol



C15 H11 Br N4 S2; Mol wt: 391.3159

ACTION – A representative compound from a series of 4-amino-3-mercapto-1,2,4-triazoles with antiproliferative and nitric oxide synthase (NOS)-inhibitory activity. Compound exhibited cytotoxicity against several human cells lines, giving IC₅₀ values of 1.3, 2.5, 8 and 5 μM against human colon carcinoma HT-29, breast cancer MCF-7, cervical cancer HeLa and skin cancer PAM 212 cells, respectively.

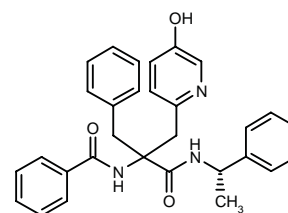
SOURCES – Competitive Technologies; State University of New Jersey, Piscataway, NJ (US).

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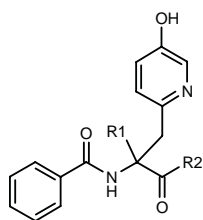
286971

*N*²-Benzoyl-2-(5-hydroxypyridin-2-ylmethyl)-*N*¹-[1(*S*)-phenylethyl]-DL-phenylalaninamide



C30 H29 N3 O3; Mol wt: 479.5771

ACTION – Antineoplastic agent, a derivative of the known agent L-azatyrosine with improved cytotoxicity, as demonstrated against human stomach cancer SC-M1 and human breast cancer BC-M1 cell lines (IC₅₀ = 0.08 and 0.6 mM, respectively, vs. 1.6 and 2.2 mM, respectively, for L-azatyrosine). Other compounds from this series of *N*-benzoyl-α-alkylated azatyrosines include the following:



Compound	R1	R2	Formula
286972	Me	OH	C ₁₈ H ₁₆ N ₂ O ₄
286973	i-Bu	OH	C ₁₉ H ₂₂ N ₂ O ₄
286974	CH ₂ Ph	OH	C ₂₂ H ₂₀ N ₂ O ₄
286975	i-Bu	OEt	C ₂₁ H ₂₆ N ₂ O ₄
286976	CH ₂ Ph	OEt	C ₂₄ H ₂₄ N ₂ O ₄
286977	i-Bu	(S)-NHCH(Me)Ph	C ₂₇ H ₃₁ N ₃ O ₃

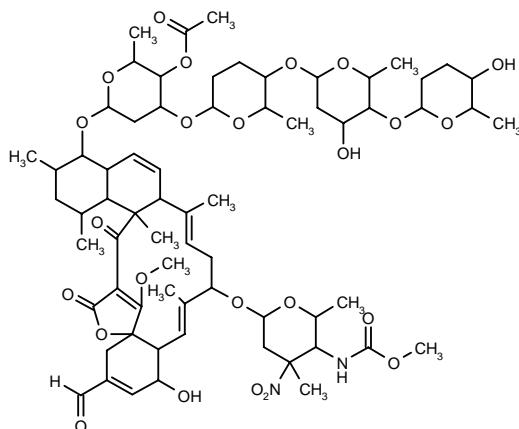
SOURCE – Unitech Pharmaceuticals.

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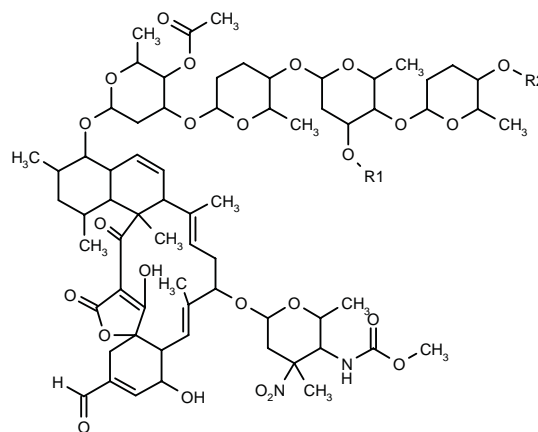
287271

17-[5-Acetoxy-4-[5-[4-hydroxy-5-(5-hydroxy-6-methyltetrahydropyran-2-yloxy)-6-methyltetrahydropyran-2-yloxy]-6-methyltetrahydropyran-2-yloxy]-6-methyltetrahydropyran-2-yloxy]-5-hydroxy-3-formyl-9-[5-(methoxycarbonylamino)-4,6-dimethyl-4-nitrotetrahydropyran-2-yloxy]-27-methoxy-8,12,18,20,22-pentamethyl-26-oxapentacyclo-[22.2.1.0^{1,6}.0^{13,22}.0^{16,21}]heptacos-3,7,11,14,24(27)-pentaene-23,25-dione



C₆₈H₉₈N₂O₂₄; Mol wt: 1327.5120

ACTION – Apoptosis-inducing and antiproliferative agent with potential in the treatment or prevention of diseases caused by the accelerated expression of proteins of the Bcl-2 family such as cancer and AIDS. Compound was found to induce apoptosis in HeLa cells and particularly in bcl-2-transfected HeLa cells, as measured by marked increases in caspase activity (169 and 1639%, respectively, at 5 μ M; controls: 100%). Furthermore, it inhibited the proliferation of HeLa/bcl-2 cells and human breast cancer MCF-7 cells with respective IC₅₀ values of 1.5 and 0.125 μ M. Some antibacterial activity was observed against *Bacillus subtilis* ATCC 10707 (MIC = 5.2 μ g/ml). Other compounds from this series of tetrocarcin derivatives include the following:



Compound	R1	R2	Formula
287272	Ac	H	C ₆₉ H ₉₈ N ₂ O ₂₅
287273	H	t-BuSi(Me) ₂	C ₇₃ H ₁₁₀ N ₂ O ₂₄ Si
287274	H	CH ₂ OMe	C ₆₉ H ₁₀₀ N ₂ O ₂₅

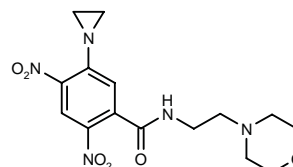
SOURCE – Kyowa Hakko.

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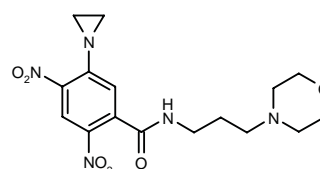
287479

5-(1-Aziridinyl)-*N*-[2-(4-morpholinyl)ethyl]-2,4-dinitrobenzamide



C₁₅H₁₉N₅O₆; Mol wt: 365.3441

ACTION – Antineoplastic agent for use in combination with a nitroreductase (NR) enzyme, preferably in antibody-directed enzyme-prodrug therapy (ADEPT) and gene-directed enzyme-prodrug therapy (GDEPT); compound acts as a prodrug that is converted to an antitumor agent by the action of nitroreductases *in vivo*. *In vitro*, it exhibited IC₅₀ values of 0.15, 0.72, 0.45 and 0.061 μ M, respectively, against NR-transformed Chinese hamster fibroblast V-79, human colon carcinoma WiDr, human ovarian carcinoma SKOV3 and murine mammary carcinoma EMT6 cells, compared to IC₅₀ values of 571, 131, 494 and 229 μ M, respectively, against the wild-type, NR-negative cell lines. Another compound from this series of nitrophenylaziridine derivatives is:



287480: C₁₆H₂₁N₅O₆

SOURCE – Cancer Research Campaign.

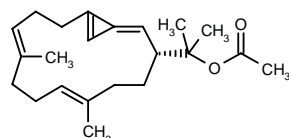
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BRASSICOLENE

287621

Acetic acid 1-[6,10-dimethylbicyclo[12.1.0]pentadeca-1,6,10,14-tetraen-3(*R*)-yl]-1-methylethyl ester



C22 H32 O2; Mol wt: 328.4928

Colorless oil, $[\alpha]_D^{25} +16.2^\circ$ (c 0.06, CHCl₃).

ACTION – Cytotoxic agent extracted from the Formosan soft coral *Nephthea brassica*. Compound exhibited cytotoxic activity against several tumor cell lines including human lung carcinoma A549 and leukemia P388 cells (IC₅₀ = 3.62 and 0.86 µg/ml, respectively).

SOURCES – Kaohsiung Medical College, Kaohsiung (TW); Sun Yat-Sen University Medical Sciences, Guangzhou (CN).

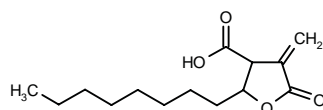
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C-75

286499

4-Methylene-2-octyl-5-oxotetrahydrofuran-3-carboxylic acid



C14 H22 O4; Mol wt: 254.3238

ACTION – Antineoplastic agent, an inhibitor of fatty acid synthase proven to inhibit [U-¹⁴C]-acetate incorporation into phospholipids and triglycerides by 87 and 89%, respectively, at 5 µg/ml in human promyelocytic leukemia HL-60 cells. In these cells, it strongly inhibited DNA replication and produced arrest of the cell cycle in S phase. Compound exhibited greater cytotoxic activity *in vitro* against human breast cancer SK-BR-3 cells (ID₅₀ = 5.0 µg/ml) versus normal human fibroblasts (ID₅₀ = 21.6 µg/ml). It also produced an increase in survival in mice bearing multidrug-resistant human ovarian cancer OVCAR-3 xenografts, a marked reduction in tumor growth in mice bearing human breast cancer MCF-7 xenografts and a marked reduction in malignant ascites in mice bearing human breast cancer MDA-435/LCC-6 xenografts.

SOURCES – Fasgen; Johns Hopkins University, Baltimore, MD (US).

REFERENCES

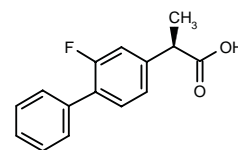
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5. Pizer, E.S. et al. *Pharmacological inhibitors of mammalian fatty acid synthase suppress DNA replication and induce apoptosis in tumor cell lines*. Cancer Res 1998, 58(20): 4611.

E-7869

274729

2(*R*)-(2-Fluorobiphenyl-4-yl)propionic acid

(*R*)-Flurbiprofen



C15 H13 F O2; Mol wt: 244.2637

ACTION – Antineoplastic agent, the (*R*)-enantiomer of the nonsteroidal antiinflammatory drug (NSAID) flurbiprofen. In animal models of cancer including prostate cancer, compound showed strong antitumor and antimetastatic activity without gastrointestinal side effects typical of NSAIDs. It does not inhibit cyclooxygenase (COX-1 or COX-2) enzymes, but appears to modulate the expression of COX-2, distinguishing it from the selective COX-2 inhibitors celecoxib and rofecoxib. In rats, mice, dogs and monkeys, compound is bioinverted to the COX-inhibitory (*S*)-enantiomer, but phase I clinical studies showed little or no bioinversion of compound in humans. Pharmacokinetic and safety studies demonstrated that compound does not accumulate with time and is well tolerated as single doses of up to 2000 mg. Phase II clinical studies in patients with prostate cancer are in progress.

SOURCES – Encore; Loma Linda University, Loma Linda, CA (US).

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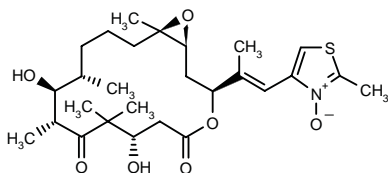
10. *Encore begins phase II trials in prostate cancer patients of its lead product.* DailyDrugNews.com (Daily Essentials) 1999, April 21.

EPOTHILONE B N-OXIDE

287527

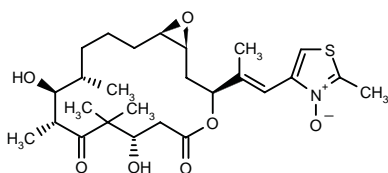
[1*R**,3*R**(*E*),7*R**,10*S**,11*R**,12*R**,16*S**]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-3-oxidothiazol-4-yl)vinyl]-4,17-dioxabicyclo[14.1.0]-heptadecane-5,9-dione

[4*R**,7*S**,8*R**,9*R**,13*S**,14*R**,16*R**(*E*)]-13,14-Epoxy-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2(*E*)-(2-methyl-3-oxidothiazol-4-yl)vinyl]-1-oxacyclohexadecane-2,6-dione



C27 H41 N O7 S; Mol wt: 523.6869

ACTION – Antineoplastic agent with potent *in vitro* cytotoxicity against murine fibroblast L929, human cervical carcinoma KB 3.1 and human lung carcinoma A549 cells (IC₅₀ = 4, 2 and 1.5 nM, respectively). Another specifically claimed compound is:



Epothilone A N-oxide [287528]: C26 H39 N O7 S

SOURCE – GBF.

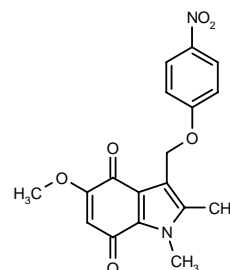
REFERENCES

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ES-936

287671

5-Methoxy-1,2-dimethyl-3-(4-nitrophenoxyethyl)-1*H*-indole-4,7-dione



C18 H16 N2 O6; Mol wt: 356.3324

ACTION – Irreversible inhibitor of human recombinant NAD(P)H dehydrogenase (quinone) (DT-diaphorase) and of enzymatic activity in cytosol prepared from human cell lines that overexpress this enzyme (98% inhibition at 25 nM in cultured human cells). Compound showed cytotoxic activity in human non-small cell lung cancer cells with either high enzyme activity or no detectable activity (IC₅₀ = 2.81 and 2.00 μM in H460 and H596 cell lines, respectively).

SOURCE – BTG.

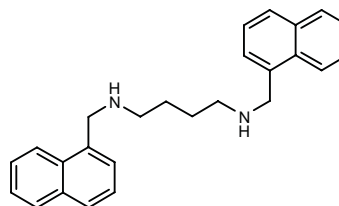
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- Stratford, I.J. et al. (BTG plc) *Indolequinone derivs. as bioreductive agents.* WO 9723456.
- Beall, H.D. et al. *Indolequinone antitumor agents: Correlation between quinone structure, rate of metabolism by recombinant human NAD(P)H:quinone oxidoreductase, and in vitro cytotoxicity.* J Med Chem 1998, 41(24): 4755.
- Winski, S.L. et al. *ES936, a novel indolequinone inhibitor of NAD(P)H:quinone oxidoreductase (NQO1).* Proc Amer Assoc Cancer Res 2000, 41: Abst 4872.

ORI-1313

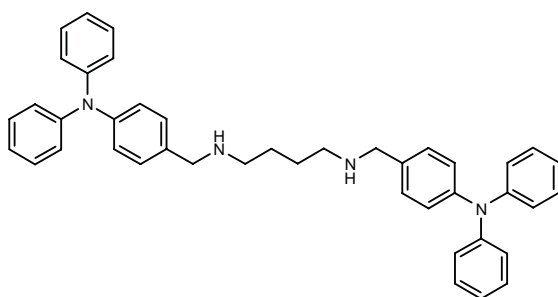
287366

*N*¹,*N*⁴-Bis(1-naphthylmethyl)butane-1,4-diamine



C26 H28 N2; Mol wt: 368.5212

ACTION – Antineoplastic agent, an analogue of the natural polyamine putrescine with selective cytotoxic activity against melanoma cell lines (IC₅₀ = 4.6 μM against SK-MEL-5 cells) and also active against a multidrug-resistant human sarcoma cell line. Compound appears to act through induction of apoptosis rather than by mechanisms typical of other polyamine analogues, i.e., depletion of intracellular polyamine levels. It was well tolerated in mice given a single dose of 92.7 mg/kg i.p. Another related compound is:



ORI-1327 [287367]: C42 H42 N4

SOURCE – Oridigm.

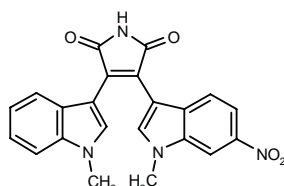
REFERENCES

1. Weeks, R.S. et al. *Analog of a biogenic amine that exhibit cytotoxicity through induction of apoptosis in multiple human tumor cell lines, including a multidrug-resistant line*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 88.

RO-31-7453

287215

3-(1-Methyl-1*H*-indol-3-yl)-4-(1-methyl-6-nitro-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione



C22 H16 N4 O4; Mol wt: 400.3924

ACTION – Antineoplastic agent, an orally active cell cycle inhibitor and apoptosis inducer. It was more potent at inhibiting cell growth ($IC_{50} = 0.02-0.30 \mu M$) than the cyclin-dependent kinases cdk1, cdk2 or cdk4 ($IC_{50} > 1 \mu M$). Compound is known to inhibit mitotic spindle formation and chromosome aggregation, induce hyperploidy and apoptosis, and inhibit progression of cells into the S phase of the cell cycle. Its antiproliferative activity is independent of tissue type, p53 function, estrogen receptor or multidrug resistance status. *In vivo*, antitumor activity has been demonstrated against a wide range of tumors and human tumor xenografts including multidrug-resistant tumors such as rat mammary adenocarcinoma MTLn-3, human breast cancer MDA-MB-435, colorectal cancer RKO, HT-29 and HCT 116, non-small cell lung cancer A549, prostate cancer DU 145, paclitaxel-resistant colorectal cancer SW480, multidrug-resistant colorectal cancer LS1034 and uterine cancer MES-SA/DX-5 xenografts. It was effective when given by various routes of administration (p.o., i.v. and i.p.) and maximal efficacy was obtained with prolonged exposure to effective concentrations. Compound was also shown to exert significant antiangiogenic activity in the mouse corneal pocket model, although marked antiangiogenic activity was associated with toxicity that consisted mainly of reversible hematological and intestinal effects. Two major metabolites —Ro-27-0431 and Ro-27-4006— exhibited similar *in vitro* activity to the parent compound and Ro-27-0431 markedly inhibited tumor growth in rats bearing rat mammary adenocarcinomas. Compound is currently in oral dose-ranging phase I clinical trials in patients with solid tumors.

SOURCE – Roche.

REFERENCES

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3. Cao, S. et al. *Antitumor efficacy and pharmacokinetics profile of Ro 31-7453 by continuous infusion in nude mice bearing human tumor xenografts*. Proc Amer Assoc Cancer Res 2000, 41: Abst 1269.
4. Cassidy, J. et al. *Phase I clinical and pharmacokinetic study of the novel cell cycle inhibitor Ro 31-7453*. Proc Am Soc Clin Oncol 2000, 19: Abst 731.
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6. Dhingra, U. et al. *Pre-clinical characterization of a new cell cycle inhibitor Ro 31-7453*. Proc Amer Assoc Cancer Res 2000, 41: Abst 218.
7. Dhingra, U. et al. *Comparison of effect of first and second course of treatment of orally administered Ro 31-7453 on efficacy and toxicity in two human xenograft models in nude mice*. Proc Amer Assoc Cancer Res 2000, 41: Abst 221.
8. Dhingra, U. et al. *Characterization of in vitro antiproliferative activity of Ro 31-7453, a new cell cycle inhibitor*. Proc Amer Assoc Cancer Res 2000, 41: Abst 198.
9. Dhingra, U. et al. *Evaluation of effects of dose and schedule on efficacy and toxicity of orally administered Ro 31-7453 in tumor bearing nude mice and Fischer 344 rats*. Proc Amer Assoc Cancer Res 2000, 41: Abst 220.
10. Dhingra, U. et al. *Identification and preclinical characterization of metabolites of Ro 31-7453, a new cell cycle inhibitor*. Proc Amer Assoc Cancer Res 2000, 41: Abst 199.
11. Dhingra, U. et al. *Ro 31-7453 has in vivo antitumor activity against human xenograft and syngeneic tumor models*. Proc Amer Assoc Cancer Res 2000, 41: Abst 219.
12. Goggin, B.S. et al. *The effect of Ro 31-7453 on the growth of MTLn3 rat mammary adenocarcinoma cells at primary and metastatic sites*. Proc Amer Assoc Cancer Res 2000, 41: Abst 217.
13. Ke, J. et al. *Computational simulation study of Ro 31-7453 exposure and anti-tumor activity*. Proc Amer Assoc Cancer Res 2000, 41: Abst 4577.
14. Nevins, T.D. et al. *Ro 31-7453 inhibits VEGF- and bFGF-induced corneal angiogenesis in the mouse*. Proc Amer Assoc Cancer Res 2000, 41: Abst 2072.
15. Soignet, S.L. et al. *A clinical and pharmacokinetic study of a novel cell cycle inhibitor (Ro 31-7453) in patients with solid tumors*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3884.

p15 BID

286766

ACTION – Polypeptide with apoptosis-promoting activity, produced by caspase cleavage of cytosolic BID in cells undergoing cell death mediated by TNF or Fas receptors; compound is reported to translocate from cell cytosol to the mitochondria and induce there the release of cytochrome c. Also disclosed are polynucleotides encoding the polypeptide, as well as vectors for its expression. Preferably, the polynucleotides are selectively delivered to target cells, for example cancer cells or virally infected cells.

SOURCE – Washington University, St. Louis, MO (US).

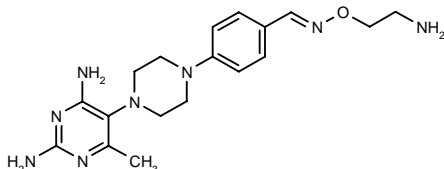
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

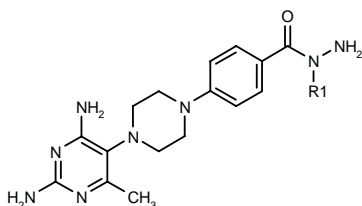
286602

4-[4-(2,4-Diamino-6-methylpyrimidin-5-yl)piperazin-1-yl]benzaldehyde *O*-(2-aminoethyl)oxime



C18 H26 N8 O; Mol wt: 370.4584

ACTION – Antineoplastic agent and multidrug resistance (MDR) modulator for use in combination with antitumor agents in the treatment of cancer, particularly P-glycoprotein-positive cancers. Like trimetrexate, compound inhibits dihydrofolate reductase, but in contrast to this compound, it is equally effective *in vitro* against P-glycoprotein-negative and -positive (doxorubicin-resistant) murine leukemia P388 cells (IC_{50} = 11 and 11.7 ng/ml, respectively, vs. 6.9 and 152 ng/ml, respectively, for trimetrexate). In addition, it was found to act synergistically with 5-fluorouracil and leucovorin in inhibiting the proliferation of human colon adenocarcinoma HT-29, sensitive and doxorubicin-resistant murine leukemia P388 and murine colon cancer C26 cells *in vitro*. Other compounds from this series of diaminopyrimidine derivatives include the following:



Compound	R1	Formula
286603	H	C ₁₈ H ₂₂ N ₈ O
286604	Me	C ₁₇ H ₂₄ N ₈ O

SOURCE – Warner-Lambert (Pfizer).

REFERENCES

- Berry, D.A. et al. (Warner-Lambert Co.) *Diaminopyrimidines and combination therapies effective for treatment of P-glycoprotein positive cancers*. WO 0009131.

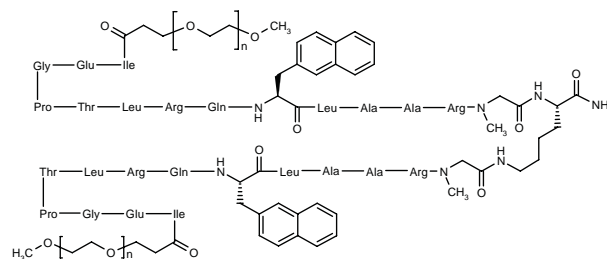
CHEMOPROTECTIVE AGENTS

GW-395058

258509

α -Hydro- ω -methoxypoly(oxy-1,2-ethanediyl) 1,1'-diether with *N*²,*N*⁶-bis[*N*-(3-hydroxypropionyl)-L-isoleucyl-L-glutamyl-glycyl-L-prolyl-L-threonyl-L-leucyl-L-arginyl-L-glutamyl-3-(2-naphthyl)-L-alanyl-L-leucyl-L-alanyl-L-alanyl-L-arginyl-*N*-methylglycyl]-L-lysineamide

GW-058



C160 H257 N45 O41(C2 H4 O)_n(C2 H4 O)_n

ACTION – Potent pegylated human thrombopoietin receptor agonist (K_i = 0.5-1.5 nM) with the ability to stimulate the proliferation and maturation of megakaryocyte colony formation *in vitro* in CD4+-enriched cell fractions purified from normal human bone marrow (EC_{50} = 0.3-0.6 nM and 3.21 pM, respectively). *In vivo*, compound was shown to stimulate platelet production in normal mice (4-fold increase in peak platelet levels at 6-8 days after a single s.c. dose of 10 μ g/kg) and to prevent chemotherapy-induced thrombocytopenia in mice. Pharmacokinetic studies in rats and monkeys demonstrated dose-related plasma exposure, with low plasma clearance and a long plasma half-life. In monkeys, the single dose required to double circulating platelet levels was 50-fold higher than that required in rats, indicating a probable species difference in the affinity for the TPO receptor. Potentially useful for the prevention of thrombocytopenia associated with chemotherapy.

SOURCE – Glaxo Wellcome.

REFERENCES

- Boyatos, C.M. et al. *Pegylated thrombopoietin-mimetic peptides elevate blood platelets and ablate the chemotherapy-induced platelet nadir in mice*. Blood 1998, 92(10, Suppl. 1, Part 1): Abst 1554.
- de Serres, M. and LaLonde, G. *Pharmacokinetics and pharmacology of the pegylated thrombopoietin peptide mimetic GW-395058 in cynomolgus and rhesus monkeys following IV or SC administration*. Annu Meet Am Assoc Pharm Sci (Nov 14-18, New Orleans) 1999, Abst 3105.
- de Serres, M. et al. *Immunogenicity of thrombopoietin mimetic peptide GW395058 in BALB/c mice and New Zealand white rabbits: Evaluation of the potential for thrombopoietin neutralizing antibody production in man*. Stem Cells 1999, 17(4): 203.
- de Serres, M. et al. *Immunogenicity studies of the thrombopoietin mimetic peptide GW395058 in Balb/c mouse, New Zealand white rabbit, and cynomolgus monkey*. Blood 1998, 92(10, Suppl. 1, Part 2): Abst 3728.
- de Serres, M. et al. *Pharmacokinetics and hematological effects of the PEGylated thrombopoietin peptide mimetic GW395058 in rats and monkeys after intravenous or subcutaneous administration*. Stem Cells 1999, 17(6): 316.

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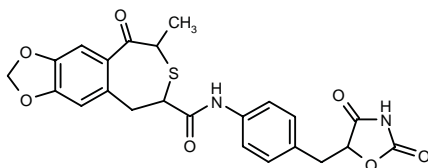
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

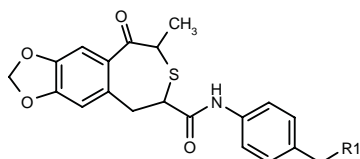
286563

N-[4-(2,4-Dioxooxazolidin-5-ylmethyl)phenyl]-8-methyl-9-oxo-5,6,8,9-tetrahydrothiepine[4,5-*f*]-1,3-benzodioxole-6-carboxamide



C23 H20 N2 O7 S; Mol wt: 468.4840

ACTION – Agent with osteogenesis- and chondrogenesis-accelerating effects whose activity was demonstrated by a significant increase in alkaline phosphatase activity in rat femoral bone marrow cells following culture for 5 days at a concentration of 10 μ M. A representative compound from a series of benzothiepin derivatives, wherein the following are also included:



Compound	R1	Formula
286564	2,4-dioxo-5-thiazolidinyl	C ₂₃ H ₂₀ N ₂ O ₆ S ₂
286565	4-morpholinyl	C ₂₄ H ₂₆ N ₂ O ₅ S
286566	3,5-dioxo-tetrahydro-1,2,4-oxadiazol-2-yl	C ₂₂ H ₁₉ N ₃ O ₇ S

SOURCE – Takeda.

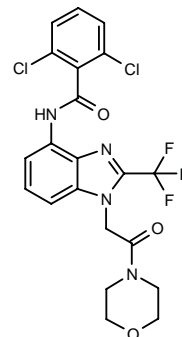
REFERENCES

1. Yasuma, T. et al. (Takeda Chemical Industries, Ltd.) *Benzothiepin derivs., process for the preparation of the same and uses thereof*. JP 2000109480, WO 0008018.

FR-177995

287034

2,6-Dichloro-*N*-[1-[2-(4-morpholinyl)-2-oxoethyl]-2-(trifluoromethyl)-1*H*-benzimidazol-4-yl]benzamide



C21 H17 Cl2 F3 N4 O3; Mol wt: 501.2903

ACTION – Bone resorption inhibitor that acts by inhibiting osteoclast vacuolar-type H⁺-ATPase (V-ATPase; IC₅₀ = 0.46 μ M) and is able to strongly inhibit bone resorption in ovariectomized rats when given orally at a dose of 3 mg/kg. Potentially useful for the treatment of postmenopausal osteoporosis.

SOURCE – Fujisawa.

REFERENCES

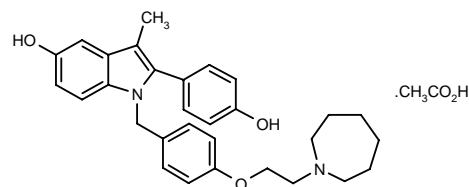
1. Oku, T. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Benzimidazole derivs. and their use in the prevention and/or the treatment of bone diseases*. EP 0863881, JP 1999513364, WO 9710219.

2. Yamazaki, H. et al. *Novel benzimidazole inhibitors of vacuolar type H⁺-ATPase*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 244.

TSE-424

257955

2-(4-Hydroxyphenyl)-3-methyl-1-[4-[2-(perhydroazepin-1-yl)ethoxy]benzyl]-1*H*-indol-5-ol acetate



C30 H34 N2 O3 . C2 H4 O2; Mol wt: 530.6612

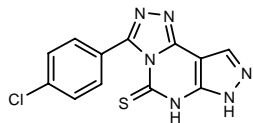
ACTION – Tissue-selective estrogen currently in phase II clinical trials for the prevention and treatment of osteoporosis in postmenopausal women. In preclinical experiments, compound demonstrated good oral activity in protecting rats from bone loss and in lowering total serum cholesterol, with little or no stimulation of rat uterus.

SOURCES – American Home Products; Ligand.

TREATMENT OF DISORDERS OF PURINE AND PYRIMIDINE METABOLISM

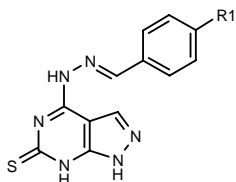
286930

3-(4-Chlorophenyl)-6,7-dihydro-5H-pyrazolo[4,3-*e*][1,2,4]-triazolo[4,3-*c*]pyrimidine-5-thione

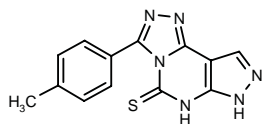


C₁₂H₇ClN₆S; Mol wt: 302.7483

ACTION – Xanthine oxidase inhibitor, as demonstrated by an IC₅₀ value of 0.054 μM for inhibition of bovine milk-derived xanthine oxidase-induced conversion of xanthine to uric acid. Other compounds from this series of pyrazolo-pyrimidine derivatives include the following:



Compound	R1	Formula
286932	H	C ₁₂ H ₁₀ N ₆ S
286933	Cl	C ₁₂ H ₉ ClN ₆ S
286934	Me	C ₁₃ H ₁₂ N ₆ S
286935	OMe	C ₁₃ H ₁₂ N ₆ OS



286931: C₁₃H₁₀N₆S

SOURCE – Yamasa Shoyu.

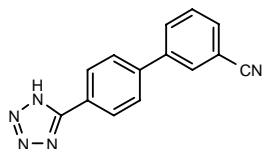
REFERENCES

1. Nagamatsu, T. et al. (Yamasa Shoyu Co., Ltd.) *Pyrazolopyrimidine cpds. and xanthine oxidase inhibitors*. JP 2000038389.

KT-651

286869

4'-(1*H*-Tetrazol-5-yl)biphenyl-3-carbonitrile



C₁₄H₉N₅; Mol wt: 247.2601

ACTION – Hypouricemic agent, an inhibitor of xanthine oxidase (IC₅₀ = 20 nM against bovine milk enzyme) shown to be about 19-fold more potent than allopurinol and at least as potent as TMX-67. In an oxonate potassium-induced hyperuricemia model in rats, compound exhibited a hypouricemic effect similar to allopurinol and TMX-67 (ED₅₀ = 9, 5 and 1 mg/kg p.o., respectively). In addition, it was found to accelerate urinary uric acid excretion in rats (ED₅₀ = 19.4 mg/kg p.o.), with superior potency to benzbromarone and probenecid. In both animal models, compound displayed a long duration of action, the effects lasting for 8-11 h.

SOURCE – Kotobuki.

REFERENCES

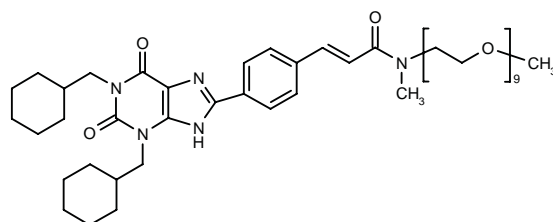
1. Tomiyama, T. et al. (Kotobuki Pharmaceutical Co., Ltd.) *Agents for the excretion of uric acid*. JP 200001431.
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DENTAL AGENTS

286627

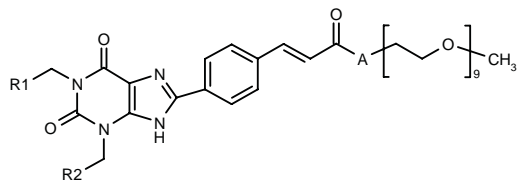
3-[4-[1,3-Bis(cyclohexylmethyl)-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-8-yl]phenyl]-*N*-methyl-*N*-(3,6,9,12,15,18,21,24,27-nonaooctacos-1-yl)-2(*E*)-propenamide

3-[4-[1,3-Bis(cyclohexylmethyl)xanthin-8-yl]phenyl]-*N*-methyl-*N*-(3,6,9,12,15,18,21,24,27-nonaooctacos-1-yl)-2(*E*)-propenamide

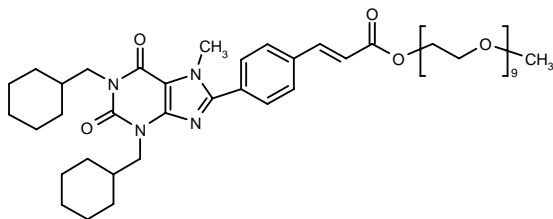


C₄₈H₇₅N₅O₁₂; Mol wt: 914.1435

ACTION – Agent for the treatment of inflammatory, immune and infectious diseases, tissue injury, cancer and other disorders characterized by altered leukocyte adhesion, and particularly periodontitis, an inhibitor of endothelial cell adhesion molecules such as ICAM-1, E-selectin, VCAM-1 and MadCAM. *In vitro*, compound inhibited the cytokine-stimulated adhesion of leukocytes to human umbilical vein endothelial cells (HUVEC) with an IC₅₀ value of 72 ± 19 nM, while *in vivo* it markedly inhibited pleural edema and neutrophil infiltration in the carrageenan pleurisy assay in rats. Other compounds from this series of glycol derivatives of xanthines include the following:



Compound	R1	R2	A	Formula
286628	cyclopentyl	cyclopentyl	-O-	C ₄₅ H ₆₈ N ₄ O ₁₃
286629	cyclohexyl	Et	-O-	C ₄₃ H ₆₆ N ₄ O ₁₃
286630	cyclohexyl	Et	-NH-	C ₄₃ H ₆₇ N ₅ O ₁₂
286631	Et	cyclohexyl	-O-	C ₄₃ H ₆₆ N ₄ O ₁₃
286632	Ph	Ph	-O-	C ₄₇ H ₆₀ N ₄ O ₁₃



286633: C48 H74 N4 O13

SOURCE – Glaxo Wellcome.

REFERENCES

1. Daluge, S.M. et al. (Glaxo Group Ltd.) *Phenyl xanthine derivs.* WO 0009507.

DIAGNOSTIC AGENTS

GADOVERSETAMIDE

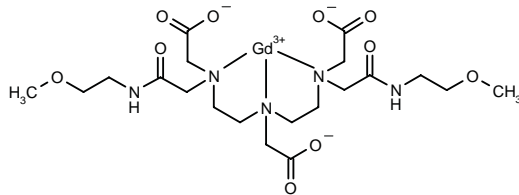
Rec INN; USAN

196021

[N,N-Bis[2-[(carboxymethyl)[N-(2-methoxyethyl)-carbamoylmethyl]amino]ethyl]glycinato(3-)]gadolinium

[8,11-Bis(carboxymethyl)-14-[2-[(2-methoxyethyl)amino]-2-oxoethyl]-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(3-)]gadolinium

Gd-DTPA-bismethoxyethylamide
MP-1177-10⁺



C20 H34 Gd N5 O10; Mol wt: 661.7720

ACTION – Contrast agent for magnetic resonance imaging (MRI), a complex formed between a chelating agent and a paramagnetic ion.

INDICATION – For use with magnetic resonance imaging (MRI) in patients with abnormal blood–brain barrier or abnormal vascularity of the brain, spine and associated tissues, as well as to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities on computed tomography.

PRESENTATION – Single-dose vials for i.v. injection containing 5, 10, 15 or 20 ml of solution, 330.9 mg/ml (0.5 mmol/ml) of gadoversetamide; syringes for i.v. injection containing 10, 15, 20 or 30 ml of solution, 330.9 mg/ml (0.5 mmol/ml) of gadoversetamide.

PROPRIETARY NAME – *OptiMARK* (US).

SOURCE – Mallinckrodt.

REFERENCES

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7. Rubin, D.L. et al. *A multicenter, randomized, double-blind study to evaluate the safety, tolerability, and efficacy of OptiMARK (gadoversetamide injection) compared with Magnevist (gadopentetate dimeglumine) in patients with liver pathology: Results of a phase III clinical trial.* J Magn Reson Imaging 1999, 9(2): 240.

8. Swan, S. et al. *Dialysis clearance of gadoversetamide (G).* 100th Annu Meet Am Soc Clin Pharmacol Ther (March 18-20, San Antonio) 1999, Abst PIII-107.

9. Swan, S.K. et al. *Pharmacokinetics, safety, and tolerability of gadoversetamide injection (OptiMARK) in subjects with central nervous system or liver pathology and varying degrees of renal function.* J Magn Reson Imaging 1999, 9(2): 317.

10. Terk, M.R. and Rozenberg, D. *Gadolinium-enhanced MR imaging of traumatic hepatic injury.* Am J Roentgenol 1998, 171(3): 665.

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12. White, D.H. et al. *Synthesis and characterization of nonionic paramagnetic metal complexes as potential magnetic resonance imaging contrast agents.* Invest Radiol 1990, 25(Suppl. 1): S56.

13. White, D.H. et al. *The thermodynamics of complexation of lanthanide (III) DTPA-bisamide complexes and their implication for stability and solution structure.* Invest Radiol 1991, 26(Suppl. 1): S226.

14. Wible, J.H. Jr. et al. *Hemodynamic effects of intravenous MP-1177/10 in anesthetized dogs.* FASEB J 1993, 7(4, Part 2): Abst 3962.

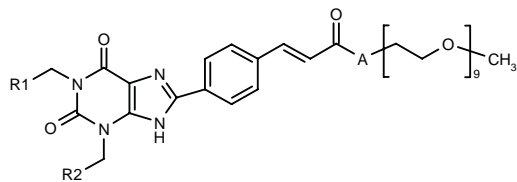
15. *Mallinckrodt launches new MRI contrast agent in U.S.* DailyDrugNews.com (Daily Essentials) 2000, April 4.

16. *Mallinckrodt's MRI contrast agent approved for marketing in U.S.* DailyDrugNews.com (Daily Essentials) 1999, Dec 13.

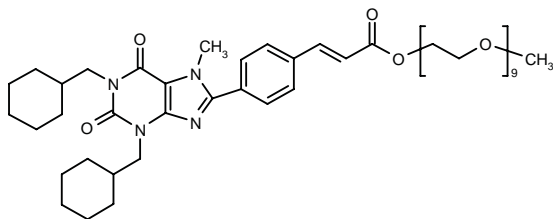
17. *New imaging agents in the pipeline at Mallinckrodt.* DailyDrugNews.com (Daily Essentials) 1998, Oct 20.

18. *Proposed international nonproprietary names (Prop. INN): List 71.* WHO Drug Inf 1994, 8(2): 96.

*Drug Data Report 1993, 015(07): 0686.



Compound	R1	R2	A	Formula
286628	cyclopentyl	cyclopentyl	-O-	C ₄₅ H ₆₈ N ₄ O ₁₃
286629	cyclohexyl	Et	-O-	C ₄₃ H ₆₆ N ₄ O ₁₃
286630	cyclohexyl	Et	-NH-	C ₄₃ H ₆₇ N ₅ O ₁₂
286631	Et	cyclohexyl	-O-	C ₄₃ H ₆₆ N ₄ O ₁₃
286632	Ph	Ph	-O-	C ₄₇ H ₆₀ N ₄ O ₁₃



286633: C48 H74 N4 O13

SOURCE – Glaxo Wellcome.

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DIAGNOSTIC AGENTS

GADOVERSETAMIDE

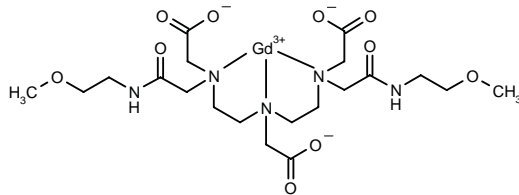
Rec INN; USAN

196021

[N,N-Bis[2-[(carboxymethyl)[N-(2-methoxyethyl)-carbamoylmethyl]amino]ethyl]glycinato(3-)]gadolinium

[8,11-Bis(carboxymethyl)-14-[2-[(2-methoxyethyl)amino]-2-oxoethyl]-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(3-)]gadolinium

Gd-DTPA-bismethoxyethylamide
MP-1177-10⁺



C20 H34 Gd N5 O10; Mol wt: 661.7720

ACTION – Contrast agent for magnetic resonance imaging (MRI), a complex formed between a chelating agent and a paramagnetic ion.

INDICATION – For use with magnetic resonance imaging (MRI) in patients with abnormal blood–brain barrier or abnormal vascularity of the brain, spine and associated tissues, as well as to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities on computed tomography.

PRESENTATION – Single-dose vials for i.v. injection containing 5, 10, 15 or 20 ml of solution, 330.9 mg/ml (0.5 mmol/ml) of gadoversetamide; syringes for i.v. injection containing 10, 15, 20 or 30 ml of solution, 330.9 mg/ml (0.5 mmol/ml) of gadoversetamide.

PROPRIETARY NAME – OptiMARK (US).

SOURCE – Mallinckrodt.

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10. Terk, M.R. and Rozenberg, D. Gadolinium-enhanced MR imaging of traumatic hepatic injury. Am J Roentgenol 1998, 171(3): 665.

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18. Proposed international nonproprietary names (Prop. INN): List 71. WHO Drug Inf 1994, 8(2): 96.

*Drug Data Report 1993, 015(07): 0686.

^{99m}Tc-**IOR CEA1**

286986

Technetium-99m (^{99m}Tc)-labeled murine IgG₁ monoclonal antibody directed against carcinoembryonic antigen (CEA)

ACTION – Diagnostic agent for cancer, a technetium-99m-labeled murine IgG₁ monoclonal antibody directed against carcinoembryonic antigen (CEA), expressed at high levels in an abnormally glycosylated form on the cell surface of human colon adenocarcinomas. Phase III clinical studies in patients with recurrent colorectal cancer demonstrated a high sensitivity of this diagnostic agent in comparison to histopathology and other diagnostic methods, with no adverse effects or hypersensitivity-type reactions.

SOURCE – Center of Molecular Immunology, Havana (CU).

REFERENCES

1. Ferro-Flores, G. and Lezama-Carrasco, J. *A freeze dried kit formulation for the preparation of ^{99m}Tc-EHDP-MoAb-IOR CEA1 complex*. Nucl Med Biol 1994, 21(7): 1013.
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3. Oliva, J.P. et al. *Ior cea1: A new monoclonal antibody anti-CEA ^{99m}Tc for immunogammagraphy of colorectal tumors. Preliminary results*. Rev Esp Med Nucl 1994, 13: 32.
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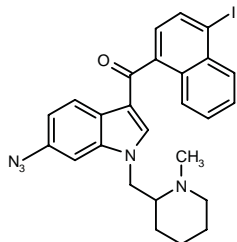
MONOGRAPH – Iznaga-Escobar, N. et al. *^{99m}Tc-ior cea1*. Drugs Fut 2000, 25(4): 0351.

PHARMACOLOGICAL TOOLS

AM-2212

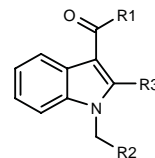
287322

1-[6-Azido-1-(1-methylpiperidin-2-ylmethyl)-1*H*-indol-3-yl]-1-(4-iodonaphthalen-1-yl)methanone



C26 H24 I N5 O; Mol wt: 549.4096

ACTION – High-affinity peripheral cannabinoid CB₂ receptor ligand ($K_i = 2.9$ nM) with 10-fold selectivity over central CB₁ receptors ($K_i = 31$ nM). Compound contains a photoactivatable azido group as the reactive group and an iodine atom which will enable labeling with I-125 for receptor-labeling experiments. Potentially useful as an affinity probe to study cannabinoid receptors. Other compounds within this series of (amino)alkylindoles are:



Compound	R1	R2	R3	Formula
AM-1205 [287037]	2-I-4-N3-Ph	Bu	H	C ₂₀ H ₁₉ IN ₄ O
AM-1215 [287038]	2-I-Ph	1-(PhCH ₂ OCO)-2-Pip	Me	C ₃₀ H ₂₉ IN ₂ O ₃
AM-2213 [287323]	4-N3-1-Naph	(CH ₂) ₃ I	H	C ₂₃ H ₁₉ IN ₄ O

AM-2213 showed the opposite profile, with respective K_i values for CB₁ and CB₂ receptors of 3.0 and 30 nM.

SOURCE – University of Connecticut, Storrs, CT (US).

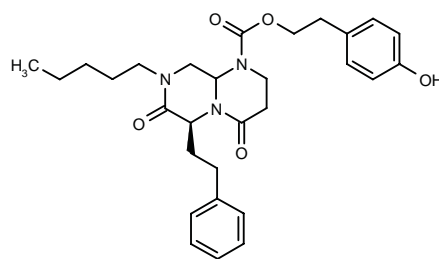
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1. Deng, H. et al. *Design, synthesis, and binding affinities of (amino)alkylindoles as affinity probes for cannabinoid receptors*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 110.

MOL-5210

287032

4,7-Dioxo-8-pentyl-6(*S*)-(2-phenylethyl)perhydropyrazino-[1,2-*a*]pyrimidine-1-carboxylic acid 2-(4-hydroxyphenyl)-ethyl ester



C29 H37 N3 O5; Mol wt: 507.6273

ACTION – Potent, nonselective opioid receptor ligand ($IC_{50} = 27$ nM) from a series of 6,6-bicyclic β -turn mimetics of enkephalin.

SOURCE – Molecumetics.

REFERENCES

1. Eguchi, M. et al. *6,6-Bicyclic beta-turn mimetics of enkephalin*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 264.

^{99m}Tc-**IOR CEA1**

286986

Technetium-99m (^{99m}Tc)-labeled murine IgG₁ monoclonal antibody directed against carcinoembryonic antigen (CEA)

ACTION – Diagnostic agent for cancer, a technetium-99m-labeled murine IgG₁ monoclonal antibody directed against carcinoembryonic antigen (CEA), expressed at high levels in an abnormally glycosylated form on the cell surface of human colon adenocarcinomas. Phase III clinical studies in patients with recurrent colorectal cancer demonstrated a high sensitivity of this diagnostic agent in comparison to histopathology and other diagnostic methods, with no adverse effects or hypersensitivity-type reactions.

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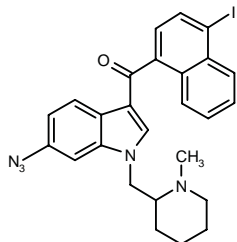
MONOGRAPH – Iznaga-Escobar, N. et al. *^{99m}Tc-ior cea1*. Drugs Fut 2000, 25(4): 0351.

PHARMACOLOGICAL TOOLS

AM-2212

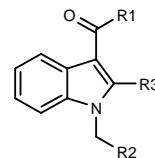
287322

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AM-2213 [287323]	4-N3-1-Naph	(CH ₂) ₃ I	H	C ₂₃ H ₁₉ IN ₄ O

AM-2213 showed the opposite profile, with respective K_i values for CB₁ and CB₂ receptors of 3.0 and 30 nM.

SOURCE – University of Connecticut, Storrs, CT (US).

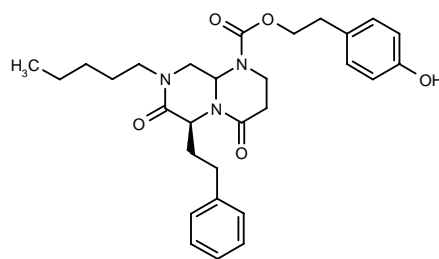
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MOL-5210

287032

4,7-Dioxo-8-pentyl-6(*S*)-(2-phenylethyl)perhydropyrazino-[1,2-*a*]pyrimidine-1-carboxylic acid 2-(4-hydroxyphenyl)-ethyl ester



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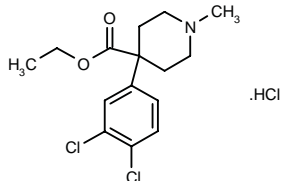
SOURCE – Molecumetics.

REFERENCES

1. Eguchi, M. et al. *6,6-Bicyclic beta-turn mimetics of enkephalin*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 264.

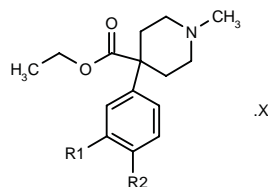
SAL-V-11^{1,2}**283970**

4-(3,4-Dichlorophenyl)-1-methylpiperidine-4-carboxylic acid ethyl ester hydrochloride



C₁₅ H₁₉ Cl₂ N O₂ . HCl; Mol wt: 352.6870

ACTION – Meperidine analogue, a potent dopamine uptake inhibitor ($K_i = 0.125 \mu\text{M}$) proven to be 142-fold more potent than meperidine ($K_i = 17.8 \mu\text{M}$). Compound also inhibits 5-HT uptake ($K_i = 0.019 \mu\text{M}$). Potentially useful as a pharmacological tool for exploring the high- and low-affinity binding sites on the dopamine transporter. Within this series of meperidine analogues, the following are also described:



Compound	R1	R2	X	Formula
SAL-IV-271 [283971]^{1,2}	-CH=CHCH=CH-	H	HCl	C ₁₉ H ₂₃ NO ₂ .HCl
SAL-IV-730 [287078]²	H	Ph		C ₂₁ H ₂₅ NO ₂

SOURCE – National Institute on Drug Abuse, Bethesda, MD (US).

REFERENCES

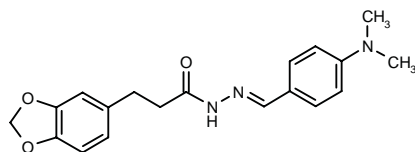
1. Lomenzo, S.A. et al. *Synthesis, dopamine and serotonin transporter binding affinities of novel analogues of meperidine*. Bioorg Med Chem Lett 1999, 9(23): 3273.
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ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

287250

3-(1,3-Benzodioxol-5-yl)propionic acid *N'*-[4-(dimethyl-amino)benzylidene]hydrazide



C19 H21 N3 O3; Mol wt: 339.3929

ACTION – Nonopioid analgesic agent, an *N*-acylaryl-hydrazone derivative with higher analgesic activity than indomethacin and dipyron in the acetic acid-induced abdominal constriction assay in mice (67.1% inhibition at 100 μ mol/kg i.p. vs. 54.9 and 35.9% inhibition, respectively, for indomethacin and dipyron at this dose).

SOURCE – Universidade Federal do Rio de Janeiro, Rio de Janeiro (BR).

REFERENCES

1. Lima, P.C. et al. *Synthesis and analgesic activity of novel N-acylarylhydrazones and isosters, derived from natural saffrole*. Eur J Med Chem 2000, 35(2): 187.

CT-3

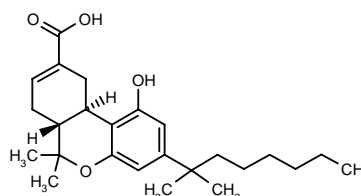
236795

(6*aR*,10*aR*)-3-(1,1-Dimethylheptyl)-1-hydroxy-6,6-dimethyl-6*a*,7,10,10*a*-tetrahydro-6*H*-benzo[*c*]chromene-9-carboxylic acid

(6*aR*,10*aR*)-3-(1,1-Dimethylheptyl)-1-hydroxy-6,6-dimethyl-6*a*,7,10,10*a*-tetrahydro-6*H*-dibenzo[*b,d*]pyran-9-carboxylic acid

1',1'-Dimethylheptyl- Δ^8 -tetrahydrocannabinol-11-oic acid

Ajulemic acid
 DMH-THC-11-OIC



C25 H36 O4; Mol wt: 400.5554

ACTION – Synthetic cannabinoid with oral antiinflammatory and analgesic activity in several preclinical models of acute and chronic inflammation. For example, it showed ED₅₀ values of 4.31 mg/kg i.v. and 1.24 mg/kg i.v., respectively, in the mouse hot-plate and *p*-phenylquinone writhing tests, as well as ED₅₀ values of 6.7 mg/kg i.g. in the mouse hot-plate assay, about 0.1 mg/kg i.g. in the mouse air pouch test, and 4.4, 11.6 and 16.4 mg/kg i.g. at 1.0, 3.0 and 5.0 h, respectively, in the mouse tail-clip test. It is also reported to exert significant activity in rats with adjuvant arthritis. In most assays, CT-3 exhibited potency similar to morphine but a more prolonged duration of action. It selectively inhibits cyclooxygenase type 2 (COX-2), and is not associated with gastric ulceration following acute administration at doses of up to 1000 mg/kg i.g., or repeated doses (5 days) of 30 mg/kg/day i.g. Compound recently entered phase I clinical trials. It has also been reported to have antiproliferative activity in tumor cell lines and to prolong survival of mice bearing glioma C6.

SOURCE – Atlantic Technology Ventures.

REFERENCES

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2. Burnstein, S.H. et al. *Synthetic nonpsychotropic cannabinoids with potent antiinflammatory, analgesic, and leukocyte antiadhesion activities*. J Med Chem 1992, 35(17): 3135.
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8. Dajani, E.Z. et al. *Analgesic and ulcerogenic investigations of CT-3 [1',1' dimethylheptyl-δ-8-THC-11-oic acid] in rats: A novel, orally effective cannabinoid*. FASEB J 1999, 13(5, Part 2): Abst 823.4.

9. Dajani, E.Z. et al. *Investigations of the analgesic actions of CT-3 [1',1' dimethylheptyl-δ-8-THC-11-oic acid] in mice: A novel, orally effective cannabinoid*. FASEB J 1999, 13(5, Part 2): Abst 823.4.

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13. *Atlantic reports analgesic effects of CT-3 in mouse model*. DailyDrugNews.com (Daily Essentials) 1999, Oct 21.

14. *Atlantic submits IND for CT-3 to FDA; phase I trials to commence in France*. DailyDrugNews.com (Daily Essentials) 2000, April 12.

15. *Atlantic to begin clinical trials of synthetic derivative of marijuana*. DailyDrugNews.com (Daily Essentials) 2000, May 11.

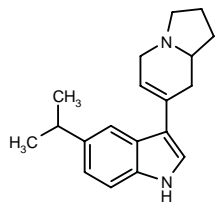
16. Atlantic Pharmaceuticals, Inc. Annual Report 1995.

17. Atlantic Pharmaceuticals, Inc. Company Profile 1996, May 10.

ANTIMIGRAINE DRUGS

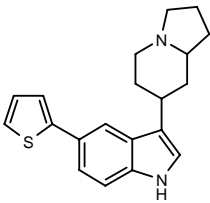
287911

3-(1,2,3,5,8,8a-Hexahydroindolizin-7-yl)-5-isopropyl-1*H*-indole



C19 H24 N2; Mol wt: 280.4126

ACTION – Selective 5-HT_{1D} receptor agonist giving > 75% inhibition of [³H]-5-HT binding to the 5-HT_{1D} receptor versus < 40% inhibition of binding to the 5-HT_{1B} receptor at 100 nM, and shown to decrease forskolin-induced cAMP production in CHO cells expressing the 5-HT_{1D} receptor at 100 nM. It is expected to be of use in the treatment of migraine. Another compound from this series of 3-bicycloindole derivatives is:



287912: C20 H22 N2 S

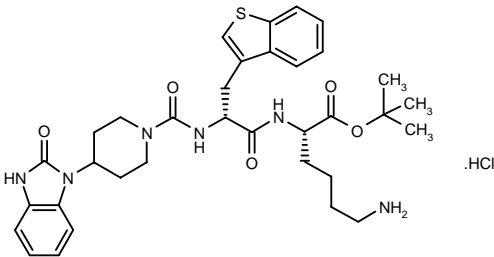
SOURCE – NPS Allelix.

REFERENCES

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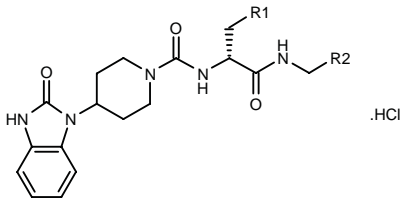
288051

N-[4-(2-Oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-ylcarbonyl]-D-(benzo[*b*]thiophen-3-yl)alanyl-L-lysine *tert*-butyl ester hydrochloride



C34 H44 N6 O5 S . HCl; Mol wt: 685.2855

ACTION – Calcitonin gene-related peptide (CGRP) receptor ligand, expected to be useful for the treatment of CGRP-associated disorders including migraine, pain, inflammatory and cardiovascular disorders, diabetes, Raynaud's syndrome, peripheral arterial insufficiency, subarachnoid and other cranial hemorrhages, and tumors. The treatment of migraine is particularly preferred. Other exemplified benzimidazoliny l piperidines include the following:



Compound	R1	R2	Formula
288052	3-benzothienyl	4-NH2-cyclohexyl	C ₃₁ H ₃₈ N ₆ O ₃ S.HCl
288053	1-Naph	3-(NH2CH2)-Ph	C ₃₄ H ₃₆ N ₆ O ₃ .HCl
288054	1-Naph	(1 <i>R</i> ,3 <i>S</i>)-3-(NH2CH2)-cyclohexyl	C ₃₄ H ₄₂ N ₆ O ₃ .HCl

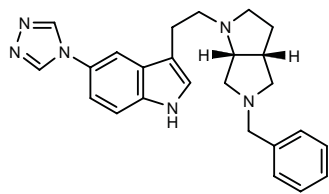
SOURCE – Merck & Co.

REFERENCES

1. Hill, R.G. et al. (Merck Sharp & Dohme Ltd.;Merck & Co., Inc.) *Benzimidazoliny l piperidines as CGRP ligands*. WO 0018764.

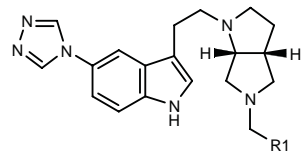
288233

cis-3-[2-(5-Benzylperhydropyrrolo[3,4-*b*]pyrrol-1-yl)ethyl]-5-(4*H*-1,2,4-triazol-4-yl)-1*H*-indole



C25 H28 N6; Mol wt: 412.5382

ACTION – Potent agonist at human 5-HT_{1Dα} (5-HT_{1D}) receptors (IC₅₀ < 50 nM) with at least 10-fold selectivity relative to 5-HT_{1Dβ} (5-HT_{1B}) receptors, expected to be useful in the treatment of migraine and associated disorders while eliciting fewer side effects than non-subtype-selective 5-HT_{1D} agonists. Other specifically claimed compounds from this series of diazabicyclooctane derivatives are:



Compound	R1	Formula
288234	CH2Ph	C ₂₆ H ₃₀ N ₆
288235	4-F-Ph	C ₂₅ H ₂₇ FN ₆
288236	2,4-(F)2-Ph	C ₂₅ H ₂₆ F ₂ N ₆

SOURCE – Merck Sharp & Dohme.

REFERENCES

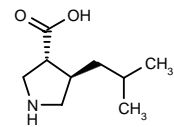
1. Madin, A. (Merck Sharp & Dohme Ltd.) *Diazabicyclooctane derivs.* US 6051591, WO 9711949.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

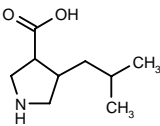
287571

4(*R*)-(Isobutyl)pyrrolidine-3(*R*)-carboxylic acid



C9 H17 N O2; Mol wt: 171.2383

ACTION – Agent for the treatment of anxiety, convulsions, pain, neurodegenerative disorders and depression that binds to the calcium channel α2-δ subunit (IC₅₀ = 0.044 μM using [³H]-gabapentin as the radioligand and porcine brain tissue) and is expected to possess activity similar to gabapentin. Other compounds from this series of branched alkyl pyrrolidine-3-carboxylic acids include the following:



Compound	Isomer	Formula
287572	S,S	C ₉ H ₁₇ NO ₂
287573	cis	C ₉ H ₁₇ NO ₂
287574	trans	C ₉ H ₁₇ NO ₂

SOURCE – Pfizer.

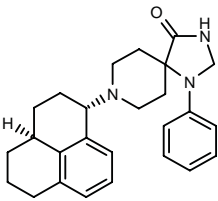
REFERENCES

1. Bryans, J.S. et al. (Warner-Lambert Co.) *Branched alkyl pyrrolidine-3-carboxylic acids.* WO 0015611.
2. Ling, R. et al. *Synthesis and biological evaluation of conformationally restricted pregabalin analogs.* 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 112.

RO-64-6198

287635

8-[(1*S*,3*aS*)-2,3,3*a*,4,5,6-Hexahydro-1*H*-phenalen-1-yl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one

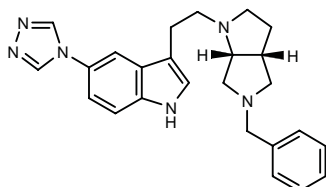


C26 H31 N3 O; Mol wt: 401.5509

ACTION – Anxiolytic agent, a selective, nonpeptide agonist at the ORL1 (N/OFQ) receptor with high affinity for the recombinant human ORL1 receptor (pK_i = 9.4) and more than 100-fold selectivity over other opioid receptors (pK_i = 7.33, 7.05 and 5.86 for human OP₃ [μ], OP₂ [κ] and OP₁ [δ] receptors, respectively); it did not show significant affinity (IC₅₀ > 1 μM) for a series of receptors and channel binding sites in brain. Compound (0.3-3 mg/kg i.p.) exhibited anxiolytic effects in several models of distinct types of anxiety states in rats including the elevated plus-maze test, the operant conflict procedure and the acoustic startle paradigm, where it exhibited efficacy and potency comparable to those of benzodiazepine anxiolytics such as diazepam or alprazolam. However, unlike benzodiazepines, compound lacks efficient anti-panic-like activity, anticonvulsant activity, as well as effects on motor performance and cognitive function, at anxiolytic doses. Although it shows low oral bioavailability, Ro-64-6198 exhibited excellent brain penetration after i.p. injection.

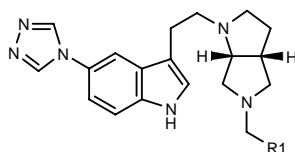
288233

cis-3-[2-(5-Benzylperhydropyrrolo[3,4-*b*]pyrrol-1-yl)ethyl]-5-(4*H*-1,2,4-triazol-4-yl)-1*H*-indole



C25 H28 N6; Mol wt: 412.5382

ACTION – Potent agonist at human 5-HT_{1Dα} (5-HT_{1D}) receptors (IC₅₀ < 50 nM) with at least 10-fold selectivity relative to 5-HT_{1Dβ} (5-HT_{1B}) receptors, expected to be useful in the treatment of migraine and associated disorders while eliciting fewer side effects than non-subtype-selective 5-HT_{1D} agonists. Other specifically claimed compounds from this series of diazabicyclooctane derivatives are:



Compound	R1	Formula
288234	CH2Ph	C ₂₆ H ₃₀ N ₆
288235	4-F-Ph	C ₂₅ H ₂₇ FN ₆
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SOURCE – Merck Sharp & Dohme.

REFERENCES

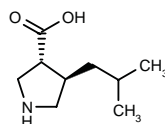
1. Madin, A. (Merck Sharp & Dohme Ltd.) *Diazabicyclooctane derivs.* US 6051591, WO 9711949.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

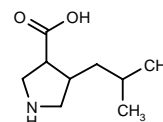
287571

4(*R*)-(Isobutyl)pyrrolidine-3(*R*)-carboxylic acid



C9 H17 N O2; Mol wt: 171.2383

ACTION – Agent for the treatment of anxiety, convulsions, pain, neurodegenerative disorders and depression that binds to the calcium channel $\alpha 2\text{-}\delta$ subunit (IC₅₀ = 0.044 μ M using [³H]-gabapentin as the radioligand and porcine brain tissue) and is expected to possess activity similar to gabapentin. Other compounds from this series of branched alkyl pyrrolidine-3-carboxylic acids include the following:



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287573	cis	C ₉ H ₁₇ NO ₂
287574	trans	C ₉ H ₁₇ NO ₂

SOURCE – Pfizer.

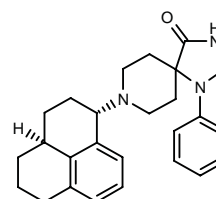
REFERENCES

1. Bryans, J.S. et al. (Warner-Lambert Co.) *Branched alkyl pyrrolidine-3-carboxylic acids.* WO 0015611.
2. Ling, R. et al. *Synthesis and biological evaluation of conformationally restricted pregabalin analogs.* 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 112.

RO-64-6198

287635

8-[(1*S*,3*aS*)-2,3,3*a*,4,5,6-Hexahydro-1*H*-phenalen-1-yl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one



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SOURCES – CeNeS; Roche.

REFERENCES

1. Adam, G. et al. (F. Hoffmann-La Roche AG) 1,3,8-Triaza-spiro 4,5 decan-4-on derivs. CA 2255171, EP 0921125, JP 1999228575.

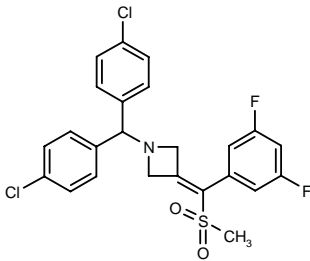
2. Adam, G. et al. (F. Hoffmann-La Roche AG) 8-Substd.-1,3,8-triazaspiro[4.5]decan-4-on derivs. EP 0856514, US 6071925.

3. Jenck, F. et al. A synthetic agonist at the orphanin FQ/nociceptin receptor ORL1: Anxiolytic profile in the rat. Proc Natl Acad Sci USA 2000, 97(9): 4938.

ANTIPSYCHOTIC DRUGS

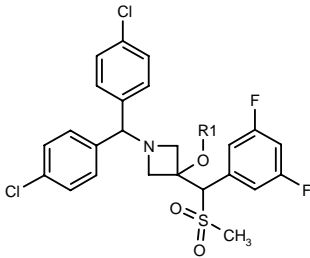
287598

1-[Bis(4-chlorophenyl)methyl]-3-[1-(3,5-difluorophenyl)-1-(methylsulfonyl)methylene]azetidine



C24 H19 Cl2 F2 N O2 S; Mol wt: 494.3871

ACTION – Cannabinoid CB₁ receptor antagonist potentially useful in the treatment or prevention of schizophrenia, anxiety, depression, epilepsy, neurodegenerative disorders, cognitive disorders, brain trauma, panic attacks, peripheral neuropathy, glaucoma, migraine, Parkinson’s disease, Alzheimer’s disease, Huntington’s chorea, obsessive–compulsive disorder, senile dementia, Tourette’s syndrome, tardive dyskinesia, as well as immune, cardiovascular, endocrine, respiratory, gastrointestinal and reproductive disorders. Other specifically claimed compounds from this series of azetidine derivatives include the following:



Compound	R1	Formula
287599	H	C ₂₄ H ₂₁ Cl ₂ F ₂ NO ₃ S
287600	Ac	C ₂₆ H ₂₃ Cl ₂ F ₂ NO ₄ S

SOURCE – Aventis Pharma.

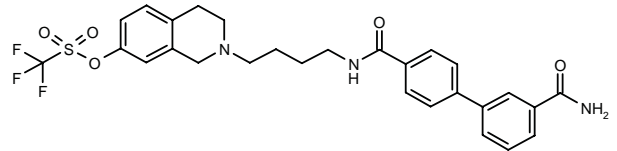
REFERENCES

1. Mignani, S. et al. (Aventis Pharma SA) Azetidine derivs., preparation and medicines containing them. FR 2783246, WO 0015609.

287715

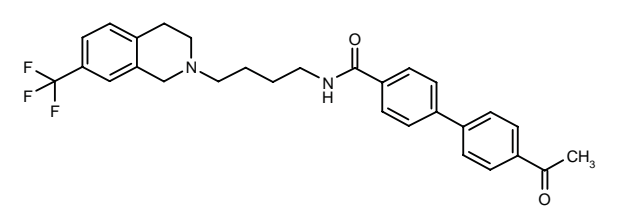
Trifluoromethanesulfonic acid 2-[4-(3'-carbamoylbiphenyl-4-ylcarboxamido)butyl]-1,2,3,4-tetrahydroisoquinolin-7-yl ester

N⁴-[4-[7-(Trifluoromethanesulfonyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl]butyl]biphenyl-4,3'-dicarboxamide



C28 H28 F3 N3 O5 S; Mol wt: 575.6052

ACTION – Dopamine D₃ receptor antagonist giving a pK_b value of 8.3-9 in a functional assay using cloned human receptors, potentially useful for the treatment of psychoses such as schizophrenia. Another exemplified compound from this series of tetrahydroisoquinoline derivatives is:



287716: C29 H29 F3 N2 O2

SOURCE – SmithKline Beecham.

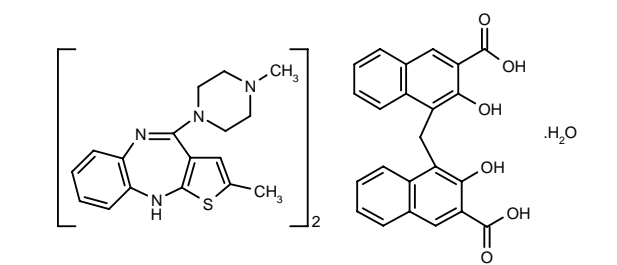
REFERENCES

1. Stemp, G. and Johns, A. (SmithKline Beecham plc) Tetrahydroisoquinoline derivs. as modulators of dopamine D₃ receptors. US 6046210, WO 9743262.

288268

Bis[2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno-[2,3-b][1,5]benzodiazepine] 4,4'-methylenebis(3-hydroxy-naphthalen-2-carboxylic acid) salt monohydrate

Bis(olanzapine) pamoate monohydrate



C23 H16 O6 . 2 C17 H20 N4 S . H2O; Mol wt: 1031.2660

ACTION – Novel salt of the antipsychotic agent olanzapine⁺ suitable for the preparation of stable, sustained-release formulations of olanzapine in which the release rate is minimally dependent on pH, particularly for use as depot formulations or for fast-acting intramuscular or subcutaneous use; this salt has the added advantage of improving drug activity per unit mass.

SOURCE – Lilly.

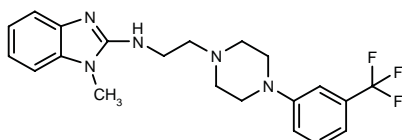
REFERENCES

1. Bunnell, C.A. et al. (Eli Lilly and Company) *2-Methyl-thieno-benzodiazepine formulation*. WO 0018408.

+Drug Data Rep 1996, 018(09): 0777.

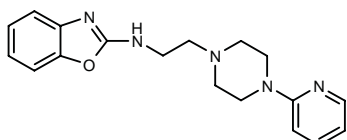
288420

N-(1-Methyl-1*H*-benzimidazol-2-yl)-*N*-[2-[4-[3-(trifluoromethyl)phenyl]piperazin-1-yl]ethyl]amine



C21 H24 F3 N5; Mol wt: 403.4496

ACTION – High-affinity and selective ligand for the dopamine D4 receptor subtype ($K_i = 3$ and $> 10,000$ nM for D4 and D2 receptor subtypes, respectively, in rat striatal homogenates) expected to be useful in the treatment or prevention of psychotic disorders such as schizophrenia, cognitive disorders, depression and other dopamine-mediated diseases. Another exemplified 2-piperazino alkyl-amino benzoxazole derivative is:



288421: C18 H21 N5 O

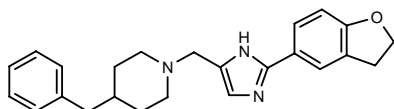
SOURCE – Neurogen.

REFERENCES

1. He, X.-S. (Neurogen Corp.) *2-Piperazino alkylamino benzoazole derivs: Dopamine receptor subtype specific ligands*. WO 0018767.

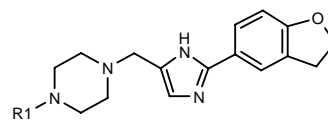
288422

4-Benzyl-1-[2-(2,3-dihydrobenzofuran-5-yl)-1*H*-imidazol-5-ylmethyl]piperidine



C24 H27 N3 O; Mol wt: 373.4973

ACTION – High-affinity and selective ligand of the dopamine D4 receptor subtype ($K_i = 15$ and > 716 nM for D4 and D2 receptor subtypes, respectively, in rat striatal homogenates) expected to be useful in the treatment or prevention of psychotic disorders such as schizophrenia, cognitive disorders, depression and other dopamine-mediated diseases. Other exemplified 2-(2,3-dihydrobenzofuran-5-yl)-4-aminomethylimidazoles are:



Compound	R1	Formula
288423	2-MeO-Ph	C ₂₃ H ₂₆ N ₄ O ₂
288424	5-Me-2-pyrimidinyl	C ₂₁ H ₂₄ N ₆ O
288425	2-quinazoliny	C ₂₄ H ₂₄ N ₆ O
288426	1-isoquinolyl	C ₂₅ H ₂₅ N ₅ O

SOURCE – Neurogen.

REFERENCES

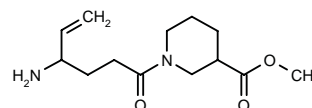
1. Chen, X. and He, X.-S. (Neurogen Corp.) *2-(2,3-Dihydrobenzofuran-5-yl)-4-aminomethylimidazoles: Dopamine receptor subtype specific ligands*. WO 0018763.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

274440

1-(4-Amino-5-hexenoyl)piperidine-3-carboxylic acid methyl ester



C13 H22 N2 O3 . C2 H F3 O2; Mol wt: 368.3497

ACTION – Anticonvulsant, a dual-acting prodrug in which vigabatrin and the GABA mimetic substance nipecotic acid are covalently coupled with an amide bond. Compound easily passed the blood–brain barrier and was rapidly hydrolyzed to the parent compounds; it protected against pentylenetetrazol-, bicuculline- and picrotoxin-induced seizures in mice ($ED_{50} = 0.15, 0.14$ and 0.10 mmol/kg i.p., respectively), whereas nipecotic acid showed no activity and vigabatrin gave ED_{50} values of 0.22 and 0.21 mmol/kg i.p. in the bicuculline and picrotoxin models, respectively. Also, compared with vigabatrin, it showed a more rapid onset of action.

SOURCE – Dong Kook.

REFERENCES

1. Je, S.-M. et al. *Design and synthesis of anticonvulsive agents as dual action prodrugs and their biological activities*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 094.

2. Kim, Y. et al. *Design and synthesis of anticonvulsive agents as γ -vinyl GABA-based potential dual acting prodrugs and their biological activities*. Bioorg Med Chem Lett 2000, 10(7): 609.

SOURCE – Lilly.

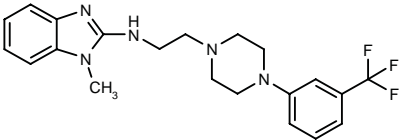
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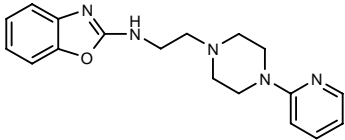
288420

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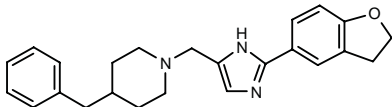
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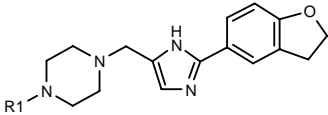
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SOURCE – Neurogen.

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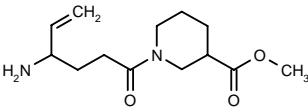
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

274440

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SOURCE – Dong Kook.

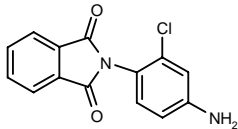
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286950

2-(4-Amino-2-chlorophenyl)-1*H*-isoindole-1,3(2*H*)-dione



C14 H9 Cl N2 O2; Mol wt: 272.6901

ACTION – Anticonvulsant found to be at least as potent as phenytoin in protecting against seizures induced by maximal electroshock in rats (ED₅₀ = 5.7 and 29.8 mg/kg p.o., respectively; ED₅₀ = 10.5 and 9.5 mg/kg i.p., respectively). Compound was also found to protect mice against magnesium deficit-dependent audiogenic seizures (ED₅₀ = 5.2 mg/kg i.p. vs. 22 mg/kg i.p. for phenytoin), without inducing neurological impairment as measured using the rotarod test (TD₅₀ > 500 mg/kg i.p. vs. 65.4 mg/kg i.p. for phenytoin). Electrophysiological studies demonstrated that compound potentiated GABA-evoked current responses but failed to directly activate the GABA_A receptor or affect NMDA-evoked potentials. In addition, it was found to interact with neuronal voltage-dependent sodium channels (IC₅₀ = 0.15 μM for inhibition of [³H]-batrachotoxin-A-20α-benzoate binding in rat synaptosomes) and to induce voltage-dependent blockade of voltage-gated sodium channels in N1E-115 neuroblastoma cells. It thus acts on both seizure spread and seizure threshold.

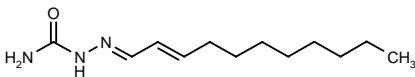
SOURCES – INSERM, Paris Cedex (FR); National Institutes of Health, Bethesda, MD (US).

REFERENCES

1. Vamecq, J. et al. *Synthesis and anticonvulsant and neurotoxic properties of substituted N-phenyl derivatives of the phthalimide pharmacophore*. J Med Chem 2000, 43(7): 1311.

287255

2-Undecenal semicarbazone



C12 H23 N3 O; Mol wt: 225.3337

ACTION – Anticonvulsant, an alkylidene semicarbazone proven to protect against maximal electroshock (MES; ED₅₀ = 21.3 mg/kg i.p.) and pentylenetetrazol-induced convulsions in mice. Although it was at least 3-fold less active than phenytoin (ED₅₀ = 6.32 mg/kg i.p.) in the MES screen, compound exhibited a higher protective index (PI [TD₅₀ in rotarod screen/ED₅₀ in MES screen] = 12.4 vs. 6.52).

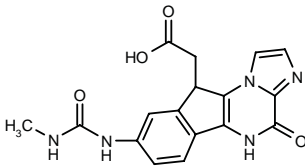
SOURCES – National Institutes of Health, Bethesda, MD (US); University of Saskatchewan, Saskatoon, SK (CA).

REFERENCES

1. Dimmock, J.R. et al. *Anticonvulsant properties of various acetylhydrazones, oxamoylhydrazones and semicarbazones derived from aromatic an unsaturated carbonyl compounds*. Eur J Med Chem 2000, 35(2): 241.

288632

(+)-8-(3-Methylureido)-4-oxo-5,10-dihydro-4*H*-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazine-10-acetic acid



C17 H15 N5 O4; Mol wt: 353.3365

ACTION – Anticonvulsant, a potent AMPA receptor antagonist (IC₅₀ = 2 nM for inhibition of currents generated by kainate in *Xenopus* oocytes) with high affinity and selectivity for this receptor versus the NMDA/glycine receptor (IC₅₀ = 0.004 and 10 μM, respectively). *In vivo*, compound exhibited potent anticonvulsant activity against maximal electroshock-induced seizures in mice and against audiogenic seizures in DBA2 mice (ED₅₀ = 1 and 0.9 mg/kg i.p., respectively).

SOURCE – Aventis Pharma.

REFERENCES

1. Aloup, J.-C. et al. (Aventis Pharma SA) *Imidazo (1,2-a)-indeno (1,2-e) pyrazin-4-one derivs. and pharmaceutical compsns. containing same*. US 5807859, WO 9526350.

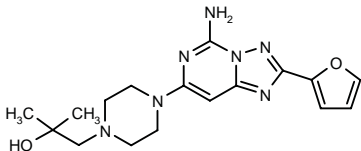
2. Mignani, S. et al. *8-Methylureido-4,5-dihydro-4-oxo-10H-imidazo[1,2-a]indeno-[1,2-e]pyrazines: Highly potent in vivo AMPA antagonists*. Bioorg Med Chem Lett 2000, 10(6): 591.

3. Stutzmann, J.-M. et al. *8-Methylureido-4-oxo-imidazo[1,2-a]indeno[1,2-e]pyrazin carboxylic acid derivatives: Highly potent and selective AMPA receptor antagonists with in vivo activity*. 27th Natl Med Chem Symp (June 13-17, Kansas City) 2000, Abst A-27.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

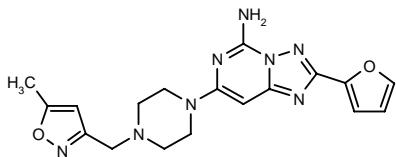
287738

1-[4-[5-Amino-2-(2-furyl)[1,2,4]triazolo[1,5-*c*]pyrimidin-7-yl]piperazin-1-yl]-2-methylpropan-2-ol



C17 H23 N7 O2; Mol wt: 357.4157

ACTION – Adenosine A_{2A} receptor antagonist that exhibits good affinity for the A_{2A} receptor in a binding assay (81 and 42% inhibition of [³H]-CGS-21680 binding in rat corpus striatum at 1 and 0.1 μM, respectively). *In vivo*, it was shown to potently inhibit CGS-21680-, halo-peridol- and reserpine-induced catalepsy in mice (72-100%) following oral administration and was found to be effective in the MPTP-induced marmoset model of Parkinson's disease. Another compound from this series of [1,2,4]triazolo[1,5-*c*]pyrimidine derivatives is:



287739: C18 H20 N8 O2

SOURCE – Kyowa Hakko.

REFERENCES

1. Shimada, J. et al. (Kyowa Hakko Kogyo Co., Ltd.) [1,2,4]Triazolo[1,5-c]pyrimidine derivs. WO 0017201.

THERAPY OF IMMUNOLOGIC NEUROMUSCULAR DISORDERS

SP-4-1

288444

Cyclized peptide with the amino acid sequence:
L-Asp-L-Ile-L-Leu-L-Met-L-Asp-L-Leu-Gly-L-Ala-L-Leu-L-Ala-L-Arg-L-Asn-L-Cys-L-Gly-L-Arg-L-Glu-L-Ser-L-Arg-L-Val-L-Asp-L-Val-L-Ala-L-Lys-L-Ser-NH₂

ACTION – Conformationally constrained peptide derived from an extracellular region of the human chemokine receptor CXCR3, useful for the preparation of vaccines for the treatment and prevention of inflammatory responses associated with autoimmune diseases such as multiple sclerosis. Compound exhibited potent binding to anti-CXCR3 antibodies in an ELISA assay and was shown to prevent experimental allergic encephalomyelitis (EAE) in mice, a model for multiple sclerosis.

SOURCE – Corixa.

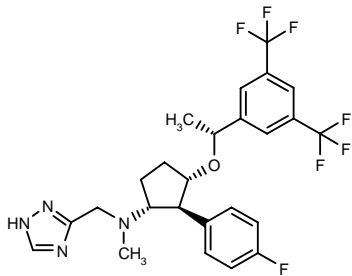
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1. Howard, M. et al. (Corixa Corp.) Chemokine receptor peptide vaccines for treatment and prevention of diabetes. WO 0018431.

TREATMENT OF NAUSEA AND VOMITING

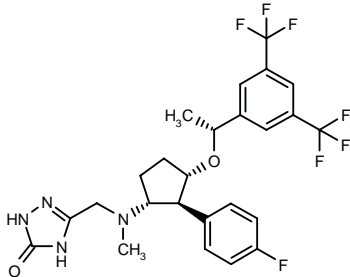
287575

(1*R*,2*S*,3*S*)-3-[1(*R*)-[3,5-Bis(trifluoromethyl)-phenyl]ethoxy]-2-(4-fluorophenyl)-*N*-methyl-*N*-(1*H*-1,2,4-triazol-3-ylmethyl)cyclopentanamine



C25 H25 F7 N4 O; Mol wt: 530.4855

ACTION – Potent human tachykinin NK₁ receptor antagonist with nanomolar affinity for NK₁ receptors (IC₅₀ = 0.18 nM), proven to inhibit the NK₁ response to peripherally released substance P (SP) in the guinea pig plasma extravasation assay with an ED₅₀ of 0.08 mg/kg p.o. Compound was able to penetrate into the CNS and inhibit foot tapping induced in gerbils by the SP agonist GR-73632 (ID₅₀ = 0.22 and 0.47 mg/kg p.o., respectively, 5 min and 24 h after administration). Potentially useful as an antiemetic and antidepressant. Another compound from this series of cyclopentane-based NK₁ antagonists is:



287576: C25 H25 F7 N4 O2

SOURCE – Merck & Co.

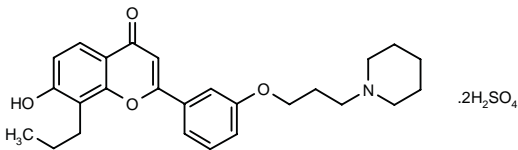
REFERENCES

1. Caldwell, C.G. et al. (Merck & Co., Inc.) Cycloalkyl tachykinin receptor antagonists. US 5750549.
2. Finke, P.E. et al. (Merck & Co., Inc.) Cyclopentyl tachykinin receptor antagonists. EP 0858444, WO 9714671.
3. Meurer, L.C. et al. Discovery of potent, orally active cyclopentane-based human NK1 antagonists. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MED1 99.

COGNITION-ENHANCING DRUGS

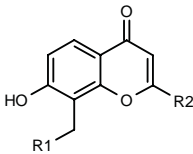
287893

7-Hydroxy-2-[3-[3-(1-piperidinyloxy)propoxy]phenyl]-8-propyl-4*H*-1-benzopyran-4-one disulfate



C26 H31 N O4 . 2 H2 O4 S; Mol wt: 617.6895

ACTION – Agent for the treatment or prevention of Alzheimer's disease and other neurodegenerative diseases by virtue of its ability to suppress the neurotoxicity of β -amyloid protein (A β) and the formation of paired helical filaments (PHF) via inhibition of tau protein kinase 1 (TPK1) phosphorylation. *In vitro*, compound gave 98.4% inhibition of P-GS1 phosphorylation by bovine cerebral TPK1. Other specifically claimed compounds from this series of hydroxyflavone derivatives are:



Compound	R1	R2	Formula
287894	Et	4-OH-3-MeO-Ph	C ₁₉ H ₁₈ O ₅
287895	H	3-[1-Pip-(CH2)3O]-Ph	C ₂₄ H ₂₇ NO ₄
287896	Et	3-[1-Pip-(CH2)3O]-4-NO2-Ph	C ₂₆ H ₃₀ N ₂ O ₆
287897	H	4-OH-3-MeO-Ph	C ₁₇ H ₁₄ O ₅
287898	Et	4-Pyr	C ₁₇ H ₁₇ NO ₂

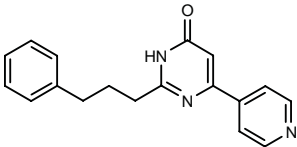
SOURCE – Mitsubishi-Tokyo Pharmaceuticals.

REFERENCES

1. Shoda, A. et al. (Mitsubishi Chemical Corp.) *Hydroxyflavone derivs. as tau protein kinase 1 inhibitors*. WO 0017184.

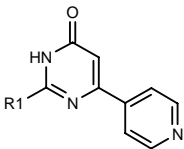
288147

2-(3-Phenylpropyl)-6-(pyridin-4-yl)pyrimidin-4(3*H*)-one



C18 H17 N3 O; Mol wt: 291.3523

ACTION – Tau protein kinase 1 (TPK1) inhibitor (IC₅₀ = 0.50 μM against bovine cerebral TPK1 phosphorylation) expected to suppress the neurotoxicity of β-amyloid protein (Aβ) and the formation of paired helical filaments (PHF), and therefore potentially useful for the treatment and/or prevention of Alzheimer’s disease and other neurodegenerative diseases. Other specifically claimed pyrimidone derivatives are:



Compound	R1	Formula
288148	3-Pyr	C ₁₄ H ₁₀ N ₄ O
288150	Ph	C ₁₅ H ₁₁ N ₃ O
288151	2-Me-Ph	C ₁₆ H ₁₃ N ₃ O
288152	3-Me-Ph	C ₁₆ H ₁₃ N ₃ O
288153	4-Me-PhCH2	C ₁₇ H ₁₅ N ₃ O
288154	4-Cl-PhCH2	C ₁₆ H ₁₂ ClN ₃ O
288155	2-thienyl-CH2	C ₁₄ H ₁₁ N ₂ OS
288156	NH2	C ₉ H ₈ N ₄ O
288157	i-BuN(Me)	C ₁₄ H ₁₈ N ₄ O

SOURCE – Mitsubishi-Tokyo Pharmaceuticals.

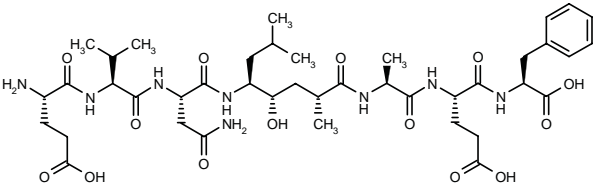
REFERENCES

1. Watanabe, K. et al. (Mitsubishi Chemical Corp.) *Pyrimidone derivs*. WO 0018758.

OM-99-2

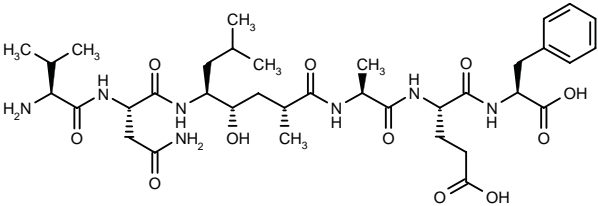
286860

L-Glutamyl-L-valyl-L-asparaginyl-L-leucyl-ψ[(*S*)-CH(OH)CH₂]-L-alanyl-L-alanyl-L-glutamyl-L-phenyl-alanine



C41 H64 N8 O14; Mol wt: 892.9986

ACTION – Potent inhibitor of the human brain aspartic protease memapsin 2 (β-secretase), giving a K_i of 9.58 nM against recombinant enzyme and about 5-fold selectivity over cathepsin D (K_i = 48 nM); it showed an inhibition profile characteristic of a tight-binding inhibitor. Selected as a lead compound for the synthesis of more active compounds with potential utility in the treatment of Alzheimer’s disease. Another related compound is:



OM-99-1 [286859]:C36 H57 N7 O11

SOURCES – University of Illinois at Chicago, Chicago, IL (US); University of Oklahoma Health Sciences Center, Oklahoma City, OK (US).

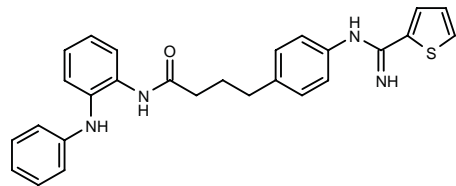
REFERENCES

1. Ghosh, A.K. et al. *Design of potent inhibitors for human brain memapsin 2 (β-secretase)*. J Am Chem Soc 2000, 122(14): 3522.

TREATMENT OF
CEREBROVASCULAR DISEASES

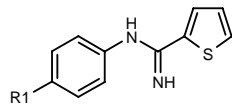
287740

4-[4-[1-Imino-1-(2-thienyl)methylamino]phenyl]-N-[2-(phenylamino)phenyl]butyramide

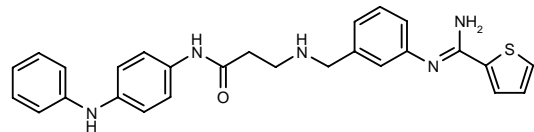


C27 H26 N4 O S; Mol wt: 454.5954

ACTION – Agent with nitric oxide synthase (NOS)-inhibitory activity (IC₅₀ < 3.5 μM against constitutive neuronal NOS from rat brain) and radical-scavenging properties, with potential in the treatment of a wide variety of pathologies such as atherosclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, asthma, migraine, cardiac and cerebral ischemia, neurodegenerative and other CNS disorders. Other specifically claimed compounds from this series of N-(iminomethyl)amine derivatives include the following:



Compound	R1	Formula
287741	4-(PhNH)-PhNHCO(CH2)3	C ₂₇ H ₂₆ N ₄ OS
287742	10H-phenothiazin-2-yl-O	C ₂₃ H ₁₇ N ₃ OS ₂
287743	10H-phenothiazin-3-yl-NHCO(CH2)3	C ₂₇ H ₂₄ N ₄ OS ₂
287745	10H-phenothiazin-3-yl-CH2NHCH2CH2	C ₂₆ H ₂₄ N ₄ S ₂



287744: C27 H27 N5 O S

SOURCE – SCRAS.

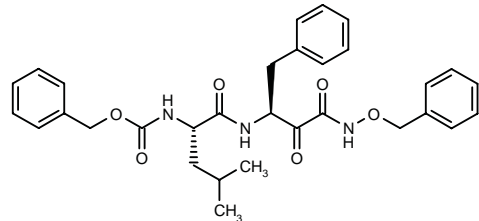
REFERENCES

1. Bigg, D. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Novel N-(iminomethyl)amine derivs., their preparation, their use as medicines and compsns. containing them.* WO 0017191.

287757

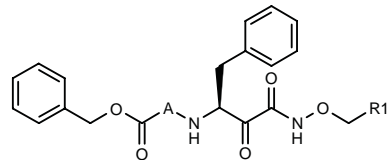
3(S)-[N-(Benzyloxycarbonyl)-L-leucinamido]-2-oxo-4-phenylbutyroxamic acid benzyl ester

N-(Benzyloxycarbonyl)-L-leucyl-L-phenylalanyl-carbohydroxamic acid benzyl ester



C31 H35 N3 O6; Mol wt: 545.6325

ACTION – An inhibitor of cysteine and serine proteases such as calpain I (IC₅₀ = 6 nM against recombinant human enzyme), with potential in the treatment of neurodegeneration, stroke, Alzheimer's disease, amyotrophy, motor neuron damage, CNS injury, muscular dystrophy, bone resorption, platelet aggregation, cataracts and inflammation. A representative compound from a series of hydroxamate derivatives, wherein the following are also included:



Compound	R1	A	Formula
287760	H	-L-Leu-	C ₂₅ H ₃₁ N ₃ O ₆
287762	Me	-L-Leu-	C ₂₆ H ₃₃ N ₃ O ₆
287763	(F)5-Ph	-L-Leu-	C ₃₁ H ₃₀ F ₅ N ₃ O ₆
287764	Ph	-L-Val-	C ₃₀ H ₃₃ N ₃ O ₆
287765	Ph	-L-Leu-L-Leu-	C ₃₇ H ₄₆ N ₄ O ₇

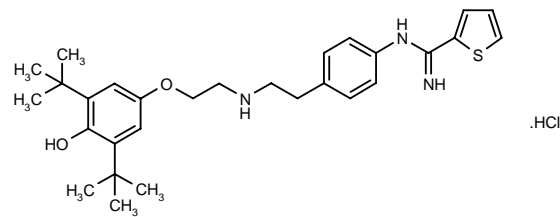
SOURCE – Cephalon.

REFERENCES

1. Mallamo, J.P. et al. (Cephalon, Inc.) *Hydroxamate-containing cysteine and serine protease inhibitors.* WO 0016767.

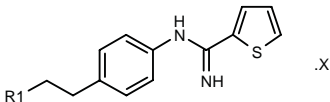
287899

N-[4-[2-[2-(3,5-Di-tert-butyl-4-hydroxyphenoxy)ethyl-amino]ethyl]phenyl]thiophene-2-carboxamide hydrochloride

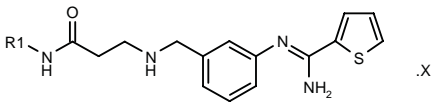


C29 H39 N3 O2 S . HCl; Mol wt: 530.1730

ACTION – Dual-action compound with inhibitory activity against nitric oxide synthase (NOS) enzymes and radical-scavenging activity, proven to inhibit constitutive neuronal enzyme (nNOS) from rat brain and lipid peroxidation in rat cerebral cortex (IC₅₀ < 3.5 and 30 μM, respectively). It may be useful in the treatment of inflammatory and proliferative diseases such as atherosclerosis, psoriasis, rheumatoid arthritis and inflammatory bowel disease, cardiovascular and cerebrovascular disorders, e.g., migraine, hypertension and cardiac or cerebral ischemia, etc. Other specifically claimed amidine derivatives are:



Compound	R1	X	Formula
287900	2-OH-5-MeO-PhNHCO	HCl	C ₂₁ H ₂₁ N ₃ O ₃ S.HCl
287906	2-OH-5-N(Me)2-PhCH2NH		C ₂₂ H ₂₆ N ₄ OS
287907	4-OH-3-MeO-PhCH=CHCH2NH	difumarate	C ₂₃ H ₂₈ N ₃ O ₂ S .2C ₄ H ₄ O ₄
287908	4-OH-3,5-(MeO)2- -PhCH=CHCH2NH	2HCl	C ₂₄ H ₂₇ N ₃ O ₃ S .2HCl
287909	6-OH-2,5,7,8-(Me)4-3,4-dihydro- -2H-benzopyran-2-yl-CH2NH		C ₂₇ H ₃₃ N ₃ O ₂ S
287910	(E)-4-OH-3,5-(MeO)2- -PhCH=CHCH2N(Me)		C ₂₅ H ₂₉ N ₃ O ₃ S



Compound	R1	X	Formula
287901	4-N(Me)2-Ph	HCl	C ₂₃ H ₂₇ N ₅ OS.HCl
287902	4-OH-3,5-(t-Bu)2-Ph	HCl	C ₂₉ H ₃₈ N ₄ O ₂ S.HCl
287903	1-Me-2,3-dihydro-5-indolyl	HCl	C ₂₄ H ₂₇ N ₅ OS.HCl
287904	1-(PhCH2)-2,3-dihydro-5-indolyl	HCl	C ₃₀ H ₃₁ N ₅ OS.HCl
287905	1-(1-Naph-CH2)-5-indolyl		C ₃₄ H ₃₃ N ₅ OS

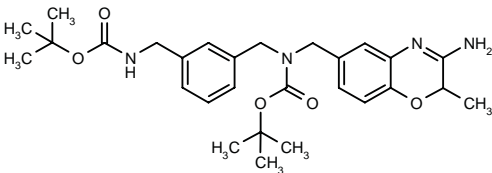
SOURCE – SCRAS.

REFERENCES

1. Auvin, S. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Novel amidine derivs., their preparation and application as medicines and pharmaceutical compsns. containing same.* FR 2783519, WO 0017190.

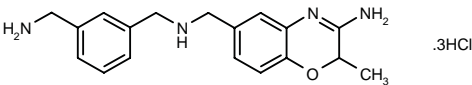
287943

N-(3-Amino-2-methyl-2*H*-1,4-benzoxazin-6-ylmethyl)-*N*-[3-(*tert*-butoxycarbonylaminomethyl)benzyl]carbamic acid *tert*-butyl ester



C28 H38 N4 O5; Mol wt: 510.6312

ACTION – Nitric oxide synthase (NOS) inhibitor for the treatment of neurodegenerative, inflammatory, auto-immune and cardiovascular disorders. Another exemplified compound from this series of benzoxazine and benzothiazine derivatives is:



287944: C18 H22 N4 O . 3HCl

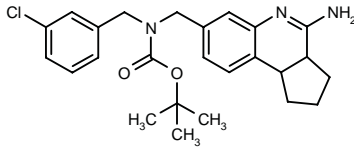
SOURCE – Schering AG.

REFERENCES

1. Hölscher, P. et al. (Schering AG) *Benzoxazine and benzothiazine derivs. and their use in medicines.* DE 19844291, WO 0017173.

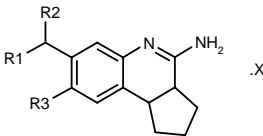
287959

N-(4-Amino-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*c*]-quinolin-7-ylmethyl)-*N*-(3-chlorobenzyl)carbamic acid *tert*-butyl ester

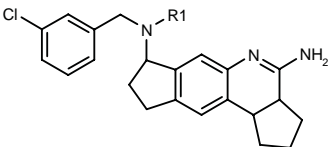


C25 H30 Cl N3 O2; Mol wt: 439.9840

ACTION – Nitric oxide synthase (NOS) inhibitor for the treatment of neurodegenerative, inflammatory, auto-immune and cardiovascular disorders. Other specifically claimed aminoalkyl-3,4-dihydroquinoline derivatives are:



Compound	R1	R2	R3	X	Formula
287960	3-Cl-PhCH2NH	H	H	2HCl	C ₂₀ H ₂₂ ClN ₃ .2HCl
287961	3-Cl-PhCH2N(t-BuOCO)CH2	H	H		C ₂₆ H ₃₂ ClN ₃ O ₂
287963	3-Cl-PhCH2NHCH2	H	H	2HCl	C ₂₁ H ₂₄ ClN ₃ .2HCl
287966	3-Cl-PhCH2N(t-BuOCO)	Et	H		C ₂₇ H ₃₄ ClN ₃ O ₂
287968	3-Cl-PhCH2NH	Et	H		C ₂₂ H ₂₆ ClN ₃
287969	3-Cl-PhCH2N(t-BuOCO)CH2	H	Cl		C ₂₆ H ₃₁ Cl ₂ N ₃ O ₂
287970	3-Cl-PhCH2NHCH2	H	Cl	2HCl	C ₂₁ H ₂₃ Cl ₂ N ₃ .2HCl



Compound	R1	Formula
287964	t-BuOCO	C ₂₇ H ₃₂ ClN ₃ O ₂
287965	H	C ₂₂ H ₂₄ ClN ₃

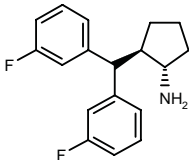
SOURCE – Schering AG.

REFERENCES

1. Jaroch, S. et al. (Schering AG) *Aminoalkyl-3,4-dihydroquinoline derivates as NO-synthase inhibitors*. DE 19845830, WO 0017167.

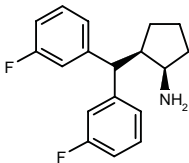
288229

trans-2-[Bis(3-fluorophenyl)methyl]cyclopentylamine



C18 H19 F2 N; Mol wt: 287.3511

ACTION – Glutamate receptor modulator that is reported to act at least in part through a novel site on the NMDA receptor-associated calcium channel, potentially useful as a neuroprotectant, anticonvulsant, anxiolytic, analgesic, muscle relaxant or as an adjuvant to general anesthetics. Compound gave an IC₅₀ value of 0.093 μM for inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells and was shown in binding assays to exhibit affinity also for the [³H]-MK-801 binding site in rat cortical/hippocampal membranes (IC₅₀ = 0.245 μM). Another specifically claimed compound from this series of arylalkylamines is:



288230: C18 H19 F2 N

SOURCE – NPS Pharmaceuticals.

REFERENCES

1. Mueller, A.L. et al. (NPS Pharmaceuticals, Inc.) *Cpds. active at a novel site on receptor-operated calcium channels useful for treatment of neurological disorders and diseases*. US 6051610.

ARTEMIN

288057

Polypeptide of the neurotrophic growth factor family

ACTION – Novel growth factor that belongs to the neurturin/persephin/GDNF (glial cell-derived neurotrophic factor) family and promotes cell survival and growth, especially of peripheral and central neurons, as demonstrated in *in vitro* studies using peripheral neurons from neonatal rats and dopaminergic neurons from the rat embryonic ventral midbrain. Like other members of the GDNF family, artemin binds to the growth factor receptor GFRα and activates the GFRα1/RET receptor complex, but it is the only member of this family that also activates the GFRα3/RET receptor complex. This polypeptide is expected to be useful in the treatment of diseases involving neuronal cell degeneration. The identification and cloning of polynucleotides encoding human and mouse artemin are also described.

SOURCE – Washington University, St. Louis, MO (US).

REFERENCES

1. Milbrandt, J.D. and Baloh, R.H. (Washington University) *Artemin, a novel neurotrophic factor*. WO 0018799.

RESPIRATORY DRUGS

ASTHMA THERAPY

287089

Antibody to the RP105 receptor

Anti-RP105 antibody

ACTION – Anti-RP105 antibody with potential in the treatment or prevention of allergic diseases including asthma and atopic dermatitis, B-cell neoplasms and autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis. *In vitro*, it was shown to significantly increase the proliferation of cultured peripheral blood lymphocytes.

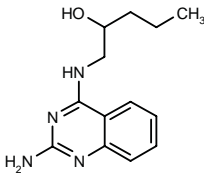
SOURCE – SmithKline Beecham.

REFERENCES

1. Harrop, J.A. et al. (SmithKline Beecham Corp.;SmithKline Beecham plc) *RP105 agonists and antagonists*. WO 0012130.

287407

1-(2-Aminoquinazolin-4-ylamino)pentan-2-ol



C13 H18 N4 O; Mol wt: 246.3122

ACTION – Agent for the treatment of allergic diseases such as asthma, allergic dermatitis and allergic rhinitis, autoimmune diseases such as systemic lupus erythematosus and AIDS that inhibits Th2-type cytokine production. *In vitro*, compound inhibited IL-4 production in murine lymph node cells with an IC₅₀ of 0.1 μM. In addition, it significantly inhibited IgE production in ovalbumin-sensitized mice when given at a dose of 3 mg/kg/day p.o. x 12 days. A representative compound from a series of quinazoline derivatives, wherein the following are also included:

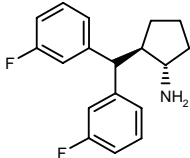
SOURCE – Schering AG.

REFERENCES

1. Jaroch, S. et al. (Schering AG) *Aminoalkyl-3,4-dihydroquinoline derivatives as NO-synthase inhibitors*. DE 19845830, WO 0017167.

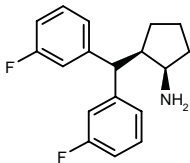
288229

trans-2-[Bis(3-fluorophenyl)methyl]cyclopentylamine



C18 H19 F2 N; Mol wt: 287.3511

ACTION – Glutamate receptor modulator that is reported to act at least in part through a novel site on the NMDA receptor-associated calcium channel, potentially useful as a neuroprotectant, anticonvulsant, anxiolytic, analgesic, muscle relaxant or as an adjuvant to general anesthetics. Compound gave an IC₅₀ value of 0.093 μM for inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells and was shown in binding assays to exhibit affinity also for the [³H]-MK-801 binding site in rat cortical/hippocampal membranes (IC₅₀ = 0.245 μM). Another specifically claimed compound from this series of arylalkylamines is:



288230: C18 H19 F2 N

SOURCE – NPS Pharmaceuticals.

REFERENCES

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ARTEMIN

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ACTION – Novel growth factor that belongs to the neurturin/persephin/GDNF (glial cell-derived neurotrophic factor) family and promotes cell survival and growth, especially of peripheral and central neurons, as demonstrated in *in vitro* studies using peripheral neurons from neonatal rats and dopaminergic neurons from the rat embryonic ventral midbrain. Like other members of the GDNF family, artemin binds to the growth factor receptor GFRα and activates the GFRα1/RET receptor complex, but it is the only member of this family that also activates the GFRα3/RET receptor complex. This polypeptide is expected to be useful in the treatment of diseases involving neuronal cell degeneration. The identification and cloning of polynucleotides encoding human and mouse artemin are also described.

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RESPIRATORY DRUGS

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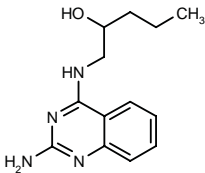
SOURCE – SmithKline Beecham.

REFERENCES

1. Harrop, J.A. et al. (SmithKline Beecham Corp.;SmithKline Beecham plc) *RP105 agonists and antagonists*. WO 0012130.

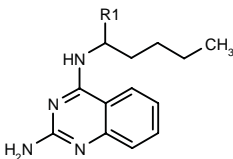
287407

1-(2-Aminoquinazolin-4-ylamino)pentan-2-ol



C13 H18 N4 O; Mol wt: 246.3122

ACTION – Agent for the treatment of allergic diseases such as asthma, allergic dermatitis and allergic rhinitis, autoimmune diseases such as systemic lupus erythematosus and AIDS that inhibits Th2-type cytokine production. *In vitro*, compound inhibited IL-4 production in murine lymph node cells with an IC₅₀ of 0.1 μM. In addition, it significantly inhibited IgE production in ovalbumin-sensitized mice when given at a dose of 3 mg/kg/day p.o. x 12 days. A representative compound from a series of quinazoline derivatives, wherein the following are also included:



Compound	R1	Formula
287408	CH2OH	C ₁₄ H ₂₀ N ₄ O
287409	CONH2	C ₁₄ H ₁₉ N ₅ O

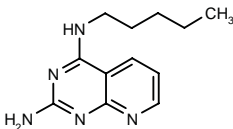
SOURCES – Sumitomo Chemical; Sumitomo Pharmaceuticals.

REFERENCES

1. Antoku, F. et al. (Sumitomo Pharmaceuticals Co., Ltd.;Sumitomo Chemical Co., Ltd.) *Quinazoline derivs.*..JP 2000053653.

287413

*N*⁴-Pentylpyrido[2,3-*d*]pyrimidine-2,4-diamine
N-(2-Aminopyrido[2,3-*d*]pyrimidin-4-yl)-*N*-pentylamine



C12 H17 N5; Mol wt: 231.3013

ACTION – An inhibitor of the production of Th2-type cytokines such as IL-4 and IL-5 with potential in the treatment of allergic diseases such as asthma, allergic dermatitis and allergic rhinitis, autoimmune diseases such as systemic lupus erythematosus and AIDS. A representative compound from a series of pyridopyrimidine derivatives.

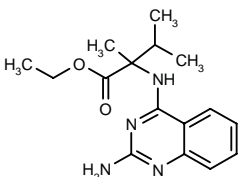
SOURCES – Sumitomo Chemical; Sumitomo Pharmaceuticals.

REFERENCES

1. Fujita, K. et al. (Sumitomo Pharmaceuticals Co., Ltd.;Sumitomo Chemical Co., Ltd.) *Pyridopyrimidine derivs.* JP 2000063381.

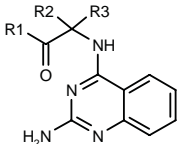
287466

2-(2-Aminoquinazolin-4-ylamino)-2,3-dimethylbutyric acid ethyl ester



C16 H22 N4 O2; Mol wt: 302.3758

ACTION – An inhibitor of the production of Th2-type cytokines such as IL-4 and IL-5 with potential in the treatment of allergic diseases such as asthma, allergic dermatitis and allergic rhinitis, autoimmune diseases such as systemic lupus erythematosus and AIDS. *In vitro*, compound was shown to inhibit IL-4 production in murine lymph node cells with an IC₅₀ of 2 μM. A representative compound from a series of quinazoline derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
287467	OEt	Et	Et	C ₁₆ H ₂₂ N ₄ O ₂
287469	OEt	Ph	Me	C ₁₉ H ₂₀ N ₄ O ₂
287470	OEt	Me	Me	C ₁₄ H ₁₈ N ₄ O ₂
287472	OEt	H	H	C ₁₂ H ₁₄ N ₄ O ₂
287474	OMe	CH2OH	H	C ₁₂ H ₁₄ N ₄ O ₃
287475	OMe	Bu	H	C ₁₅ H ₂₀ N ₄ O ₂
287476	OEt	Me	H	C ₁₃ H ₁₆ N ₄ O ₂
287477	OEt	i-Bu	H	C ₁₆ H ₂₂ N ₄ O ₂
287478	Pr	H	H	C ₁₃ H ₁₆ N ₄ O

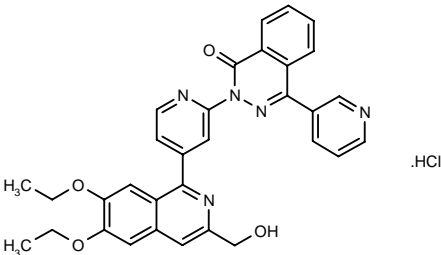
SOURCES – Sumitomo Chemical; Sumitomo Pharmaceuticals.

REFERENCES

1. Tokunaga, T. et al. (Sumitomo Pharmaceuticals Co., Ltd.;Sumitomo Chemical Co., Ltd.) *Novel quinazoline derivs.* JP 2000053654.

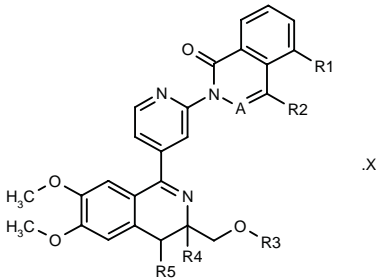
287468

2-[4-[6,7-Diethoxy-3-(hydroxymethyl)isoquinolin-1-yl]pyridin-2-yl]-4-(3-pyridyl)phthalazin-1(2*H*)-one hydrochloride

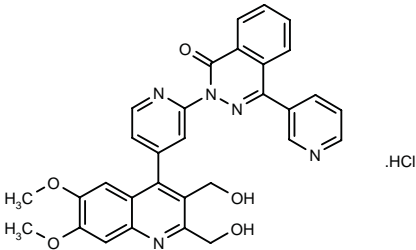


C32 H27 N5 O4 . HCl; Mol wt: 582.0572

ACTION – Selective inhibitor of phosphodiesterase type 4 (PDE4) and antihistaminic agent for the treatment of asthma. It inhibited partially purified PDE4 with an IC₅₀ of 0.0004 μM and histamine-induced bronchoconstriction in guinea pigs by 97% at 1 mg/kg i.d. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	A	X	Formula
287471	H	Me	H	bond	N			C ₂₆ H ₂₂ N ₄ O ₄
287473	H	2-thiazolyl	H	bond	N			C ₂₈ H ₂₁ N ₅ O ₄ S
287481	H	H	H	bond	N			C ₂₅ H ₂₀ N ₄ O ₄
287482	H	3-Pyr	Ac	H	H	N		C ₃₂ H ₂₇ N ₅ O ₅
287484	H	3-Pyr	H	H	H	N		C ₃₀ H ₂₅ N ₅ O ₄
287485	4-morpholinyl- -CH ₂ CH ₂ O	H	H	H	H	CH	HCl	C ₃₂ H ₃₄ N ₄ O ₆ .HCl
287487	H	3-Pyr	H	H	H	N	HCl	C ₃₀ H ₂₅ N ₅ O ₄ .HCl



287488: C₃₁ H₂₅ N₅ O₅ . HCl

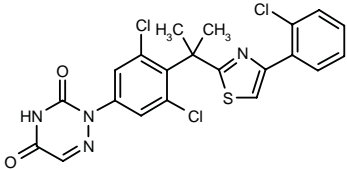
SOURCE – Tanabe Seiyaku.

REFERENCES

1. Ukida, T. et al. (Tanabe Seiyaku Co., Ltd.) *Medicinal compsns.* JP 2000063275.

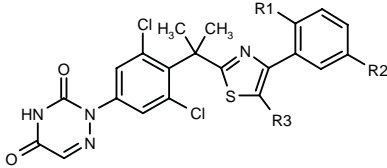
287533

2-[3,5-Dichloro-4-[1-[4-(2-chlorophenyl)thiazol-2-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione

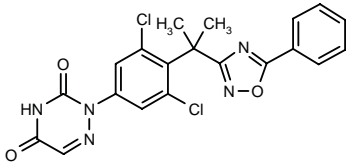


C₂₁ H₁₅ Cl₃ N₄ O₂ S; Mol wt: 493.8005

ACTION – Agent for the treatment of eosinophil-dependent inflammatory diseases such as bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis that acts by inhibiting IL-5 production (94% inhibition in phytohemagglutinin-stimulated human whole blood at 1 µM). Other exemplified compounds from this series of 6-azauracil derivatives include the following:



Compound	R1	R2	R3	Formula
287534	H	H	CO ₂ Et	C ₂₄ H ₂₀ Cl ₂ N ₄ O ₄ S
287535	H	F	Me	C ₂₂ H ₁₇ Cl ₂ FN ₄ O ₂ S
287536	H	H	CH ₂ OMe	C ₂₃ H ₂₀ Cl ₂ N ₄ O ₃ S
287537	F	H	Ph	C ₂₇ H ₁₉ Cl ₂ FN ₄ O ₂ S
287538	Me	H	Ph	C ₂₈ H ₂₂ Cl ₂ N ₄ O ₂ S



287540: C₂₀ H₁₅ Cl₂ N₅ O₃

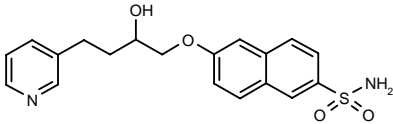
SOURCE – Janssen.

REFERENCES

1. Freyre, E.J.E. et al. (Janssen Pharmaceutica NV) *Interleukin-5 inhibiting 6-azauracil derivs.* EP 0987265, WO 0017195.

288258

6-[2-Hydroxy-4-(3-pyridinyl)butoxy]naphthalene-2-sulfonamide



C₁₉ H₂₀ N₂ O₄ S; Mol wt: 372.4430

ACTION – Inhibitor of the activation of a range of cell types from the hematopoietic lineage including mast cells, neutrophils and eosinophils, found to inhibit histamine release in primate bronchoalveolar mast cells (IC₅₀ < 0.1 mM). Potentially useful for the treatment or prophylaxis of allergic, inflammatory, autoimmune and proliferative diseases, particularly reversible obstructive airways disease and especially asthma and rhinitis.

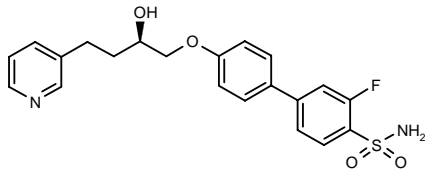
SOURCE – AstraZeneca.

REFERENCES

1. Cheshire, D. (Astra Pharmaceuticals, Ltd.; Astra AB) *Novel cpds.* WO 0018736.

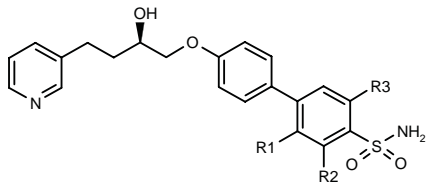
288269

3-Fluoro-4'-[2(*R*)-hydroxy-4-(3-pyridyl)butoxy]biphenyl-4-sulfonamide



C21 H21 F N2 O4 S; Mol wt: 416.4709

ACTION – Inhibitor of the activation of a range of cell types from the hematopoietic lineage including mast cells, neutrophils and eosinophils, found to inhibit histamine release in primate bronchoalveolar mast cells (IC₅₀ < 0.1 mM). Potentially useful for the treatment or prophylaxis of allergic, inflammatory, autoimmune and proliferative diseases, particularly reversible obstructive airways disease and especially asthma and rhinitis. Other specifically claimed pyridyl derivatives are:



Compound	R1	R2	R3	Formula
288270	F	H	F	C ₂₁ H ₂₀ F ₂ N ₂ O ₄ S
288271	F	H	H	C ₂₁ H ₂₁ FN ₂ O ₄ S
288272	H	F	F	C ₂₁ H ₂₀ F ₂ N ₂ O ₄ S
288273	H	H	H	C ₂₁ H ₂₂ N ₂ O ₄ S

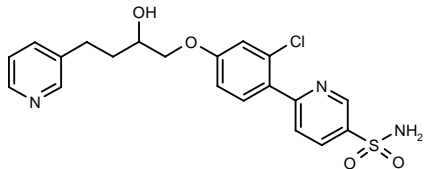
SOURCE – AstraZeneca.

REFERENCES

1. Cheshire, D. and Stocks, M. (Astra Pharmaceuticals, Ltd.; Astra AB) *Novel cpds.* WO 0018730.

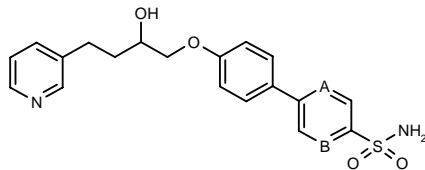
288274

6-[2-Chloro-4-[2-hydroxy-4-(3-pyridyl)butoxy]phenyl]-pyridine-3-sulfonamide



C20 H20 Cl N3 O4 S; Mol wt: 433.9140

ACTION – Inhibitor of the activation of a range of cell types from the hematopoietic lineage including mast cells, neutrophils and eosinophils, found to inhibit histamine release in primate bronchoalveolar mast cells (IC₅₀ < 0.1 mM). Potentially useful for the treatment or prophylaxis of allergic, inflammatory, autoimmune and proliferative diseases, particularly reversible obstructive airways disease and especially asthma and rhinitis. Other specifically claimed pyridyl derivatives are:



Compound	A	B	Isomer	Formula
288275	N	CH		C ₂₀ H ₂₁ N ₃ O ₄ S
288276	CH	N	R	C ₂₀ H ₂₁ N ₃ O ₄ S

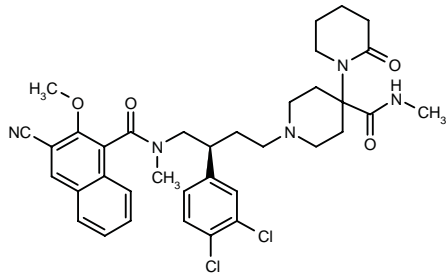
SOURCE – AstraZeneca.

REFERENCES

1. Cheshire, D. and Furber, M. (Astra Pharmaceuticals, Ltd.; Astra AB) *Novel cpds.* WO 0018731.

288459

1-[4-[*N*-(3-Cyano-2-methoxy-1-naphthylcarbonyl)-*N*-methylamino]]-3(*S*)-(3,4-dichlorophenyl)butyl]-*N*-methyl-4-(2-oxo-piperidin-1-yl)piperidine-4-carboxamide



C36 H41 Cl2 N5 O4; Mol wt: 678.6569

ACTION – Tachykinin receptor antagonist particularly active at NK₁ and NK₂ receptors, potentially useful for the treatment of asthma, as well as other NK₁/NK₂-related disorders such as rheumatoid arthritis, Alzheimer's disease, cancer, schizophrenia, edema, allergic rhinitis, inflammation, pain, gastrointestinal hypermotility, anxiety, emesis, Huntington's disease, psychoses, hypertension, migraine, bladder hypermotility or urticaria.

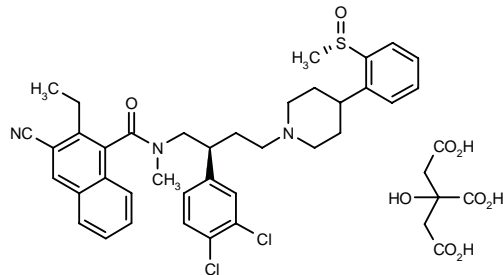
SOURCE – AstraZeneca.

REFERENCES

1. Bernstein, P.R. et al. (Zeneca, Ltd.) *Naphthalenecarboxamides as tachykinin receptor antagonists.* WO 0020003.

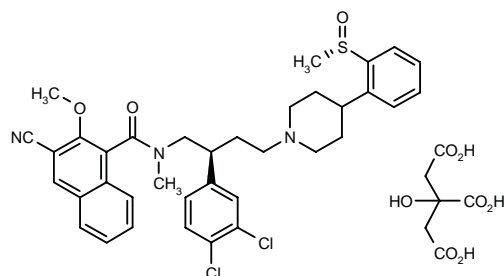
288460

3-Cyano-*N*-[2(*S*)-(3,4-dichlorophenyl)-4-[4-[2-[(*S*)-methylsulfinyl]phenyl]piperidin-1-yl]butyl]-2-ethyl-*N*-methylnaphthalene-1-carboxamide citrate



C37 H39 Cl2 N3 O2 S . C6 H8 O7; Mol wt: 852.8283

ACTION – Tachykinin receptor antagonist particularly active at NK₁ and NK₂ receptors ($pK_b = 9.6$ and 7.3 , respectively, in rabbit pulmonary artery). Potentially useful for the treatment of asthma, as well as other NK₁/NK₂-related disorders such as rheumatoid arthritis, Alzheimer's disease, cancer, schizophrenia, edema, allergic rhinitis, inflammation, pain, gastrointestinal hypermotility, anxiety, emesis, Huntington's disease, psychoses, hypertension, migraine, bladder hypermotility or urticaria. Another exemplified naphthalenecarboxamide is:



288461: C₃₆ H₃₇ Cl₂ N₃ O₃ S . C₆ H₈ O₇

SOURCE – AstraZeneca.

REFERENCES

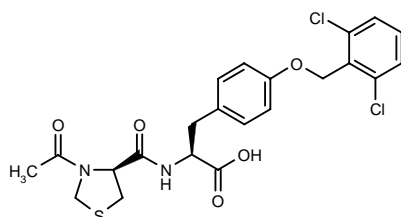
1. Bernstein, P.R. et al. (Zeneca, Ltd.) *Naphthalenecarboxamides as tachykinin receptor antagonists*. WO 0020389.

CT-5219*

271910

N-Acetyl-4-thia-D-prolyl-[4-*O*-(2,6-dichlorobenzyl)]-L-tyrosine

N-[3-Acetyl-4(*S*)-thiazolidinylcarbonyl]-L-[4-*O*-(2,6-dichlorobenzyl)]-tyrosine



C₂₂ H₂₂ Cl₂ N₂ O₅ S; Mol wt: 497.3968

ACTION – Potent, low-molecular-weight VLA-4 antagonist ($IC_{50} = 2$ nM) proven to inhibit antigen-induced airways responses in rabbit and sheep models of asthma. In the rabbit model, compound at a dose of 10 mg/kg i.v. given 1 h before antigen challenge produced significant reductions in immediate bronchoconstriction (55%) and broncho-alveolar lavage eosinophilia (85%), as well as complete inhibition of airways hyperresponsiveness to histamine at 24 h. In allergic sheep, compound at 0.03-3.0 mg/kg i.v. given 1 h before antigen challenge dose-dependently reduced both early- and late-phase responses and airways hyperresponsiveness to carbachol at 24 h. In the same model, an oral dose of 30 mg/kg 2 h before antigen produced over 80% inhibition of all responses. Potentially useful for the treatment of bronchial asthma.

SOURCE – Celltech Group.

REFERENCES

1. Head, J.C. et al. (Celltech Chiroscience plc) *Anti-inflammatory tyrosine derivs*. EP 0984981, WO 9854207.
2. Archibald, S.C. et al. *Discovery and evaluation of potent, tyrosine-based $\alpha4\beta1$ integrin antagonists*. Bioorg Med Chem Lett 2000, 10(9): 997.
3. Gozzard, N. et al. *CT5219, a low molecular weight antagonist of the integrin $\alpha4\beta1$ (VLA-4) inhibits antigen-induced airway responses in rabbit and sheep models of asthma*. Am J Respir Crit Care Med 2000, 161(3, Part 2): A841.
4. Norman, P. *Rational approaches to new drug design in the U.K.* Drug News Perspect 2000, 013(04): 0245.

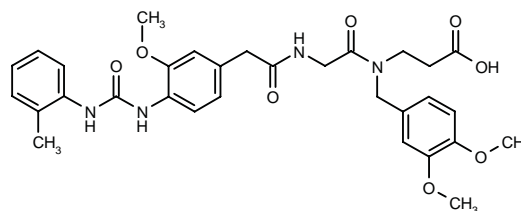
*Identified compound **271910** Drug Data Rep 1999, 021(03): 0255.

IVL-745*

278613

3-[*N*-(3,4-Dimethoxybenzyl)-*N*-[2-[2-[3-methoxy-4-[3-(2-methylphenyl)ureido]phenyl]acetamido]acetyl]amino]-propionic acid

N-(3,4-Dimethoxybenzyl)-*N*-[2-[2-[3-methoxy-4-[3-(2-methylphenyl)ureido]phenyl]acetyl]glycyl]- β -alanine



C₃₁ H₃₆ N₄ O₈; Mol wt: 592.6454

ACTION – Potent and selective VLA-4 antagonist that inhibits VLA-4-dependent cell adhesion, as demonstrated by nanomolar efficacy in several assays. Compound also produced concentration-dependent inhibition of the proliferation of human T-cells induced by recombinant human VCAM-1 ($IC_{50} = 5.7$ nM), as well as IL-2 and IL-5 release ($IC_{50} = 3.24$ and 237 nM, respectively), whereas it had no effect on anti-CD3- or anti-CD28-induced proliferation and cytokine release. In sensitized Brown-Norway rats challenged with ovalbumin, doses of 3 and 10 mg/kg given intratracheally 30 min prior to and 4 h following challenge improved lung histopathological changes and reduced eosinophil and lymphomononuclear cell infiltration into the airways; airways inflammation was inhibited when compound was administered 30 min, 4 and 6 h before ovalbumin challenge, as well as 4 h after antigen. Pharmacokinetic studies showed rapid and sustained exposure to the drug, resulting in inhibition of airways inflammation for up to 8 h. Potentially useful for the treatment of bronchial asthma.

SOURCE – Aventis Pharma.

REFERENCES

1. Astles, P.C. et al. (Rhône-Poulenc Rorer Ltd.) *Subst. β -alanines*. WO 9933789.
2. Bhatta, P. et al. *The VLA-4 antagonist IVL745 is a novel and potent inhibitor of human lymphocyte adhesion to VCAM-1*. Am J Respir Crit Care Med 2000, 161(3, Part 2): A201.
3. Cairns, J.A. et al. *The VLA-4 antagonist IVL 745 is a novel and potent inhibitor of eosinophil adhesion to VCAM-1*. Am J Respir Crit Care Med 2000, 161(3, Part 2): A202.

4. Ebsworth, K. et al. *The VLA-4 antagonist IVL745 is a novel and potent inhibitor of VCAM-1 co-stimulated human T-cell activation.* Am J Respir Crit Care Med 2000, 161(3, Part 2): A201.

5. Lockey, P. et al. *IVL 745, a potent, selective, low molecular weight antagonist of VLA-4 mediated cell adhesion.* Am J Respir Crit Care Med 2000, 161(3, Part 2): A201.

6. Sargent, C.A. et al. *In vivo profile of the novel VLA 4 antagonist IVL745 in antigen induced airway inflammation in the rat.* Am J Respir Crit Care Med 2000, 161(3, Part 2): A199.

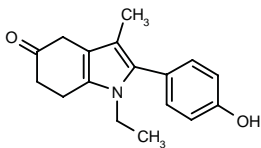
*Identified compound **278613** Drug Data Rep 1999, 021(09): 0782.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

287414

1-Ethyl-2-(4-hydroxyphenyl)-3-methyl-4,5,6,7-tetrahydro-1*H*-indol-5-one



C17 H19 N O2; Mol wt: 269.3421

ACTION – Endothelin-converting enzyme (ECE) inhibitor (IC₅₀ = 16.0 μM against rat lung enzyme), a representative compound from a series of pyrrole derivatives with potential in the treatment of circulatory disorders such as hypertension and arteriosclerosis.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Hasegawa, H. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Pyrrole derivs.* JP 2000063354.

AS-AT1R-ODN-mRNA

288144

Antisense oligodeoxynucleotide targeted to AT₁ receptor mRNA whose sequence is: 5'-TAACTGTGCCTGCCA-3'

ACTION – Antihypertensive agent, an antisense oligodeoxynucleotide targeted to angiotensin type 1 receptor mRNA. In rats with abdominal aortic banding, compound given i.v. in liposomal carriers was shown to significantly reduce mean arterial and systolic blood pressure, as well as left ventricular weight/body weight ratios. In this model, compound also induced reductions in myocardial atrial natriuretic peptide (ANP) mRNA and sarcoplasmic reticulum Ca²⁺-ATPase.

SOURCE – University of Florida, Gainesville, FL (US).

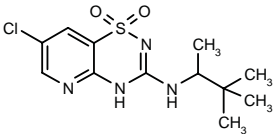
REFERENCES

1. Schmidt-Ott, K.M. et al. *Reduction of cardiac damage with AT1-R antisense.* FASEB J 2000, 14(4): Abst 309.2.

BPDZ-83²

288062

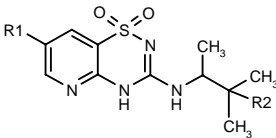
7-Chloro-3-(1,2,2-trimethylpropylamino)-4*H*-pyrido[2,3-*e*]-[1,2,4]thiadiazine 1,1-dioxide



C12 H17 Cl N4 O2 S; Mol wt: 316.8113

M.p. > 300 °C.

ACTION – ATP-sensitive potassium (K_{ATP}) channel opener with a pharmacological profile similar to that of pinacidil and diazoxide. Compound induced relaxation in rat aortic rings precontracted with 30 mM KCl (EC₅₀ = 2.3 μM) and its activity was strongly reduced when the concentration of KCl increased to 80 mM (EC₅₀ = 33 μM); in the presence of increasing concentrations of the K_{ATP} channel blocker glibenclamide, a concentration-dependent decrease in the myorelaxant efficiency of the compound was seen. It was selective for vascular smooth muscle tissue, being inactive on both electrically stimulated guinea pig ileum and oxytocin-contracted rat uterus. Potentially useful as an antihypertensive agent. Within this class of 3-alkylamino-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxides, the following are also included:



Compound	R1	R2	Formula
BPDZ-79 [251640] ^{1,2}	H	Me	C ₁₂ H ₁₈ N ₄ O ₂ S
288060	H	H	C ₁₁ H ₁₆ N ₄ O ₂ S
288061	Cl	H	C ₁₁ H ₁₅ ClN ₄ O ₂ S

SOURCES – Université Libre de Bruxelles, Bruxelles (BE); University of Liège, Liège (BE).

REFERENCES

1. Fang, Z.-Y. et al. *Vasodilative properties of BPDZ 79, a new potassium channel opener, in isolated aorta.* Acta Pharmacol Sin 1997, 18(2): 101.

2. Pirotte, B. et al. *3-Alkylamino-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxides structurally related to diazoxide and pinacidil as potassium channel openers acting on vascular smooth muscle cells: Design, synthesis, and pharmacological evaluation.* J Med Chem 2000, 43(8): 1456.

4. Ebsworth, K. et al. *The VLA-4 antagonist IVL745 is a novel and potent inhibitor of VCAM-1 co-stimulated human T-cell activation*. Am J Respir Crit Care Med 2000, 161(3, Part 2): A201.

5. Lockey, P. et al. *IVL 745, a potent, selective, low molecular weight antagonist of VLA-4 mediated cell adhesion*. Am J Respir Crit Care Med 2000, 161(3, Part 2): A201.

6. Sargent, C.A. et al. *In vivo profile of the novel VLA 4 antagonist IVL745 in antigen induced airway inflammation in the rat*. Am J Respir Crit Care Med 2000, 161(3, Part 2): A199.

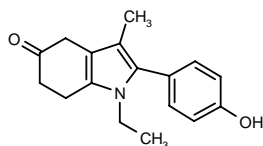
*Identified compound **278613** Drug Data Rep 1999, 021(09): 0782.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

287414

1-Ethyl-2-(4-hydroxyphenyl)-3-methyl-4,5,6,7-tetrahydro-1*H*-indol-5-one



C17 H19 N O2; Mol wt: 269.3421

ACTION – Endothelin-converting enzyme (ECE) inhibitor ($IC_{50} = 16.0 \mu M$ against rat lung enzyme), a representative compound from a series of pyrrole derivatives with potential in the treatment of circulatory disorders such as hypertension and arteriosclerosis.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Hasegawa, H. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Pyrrole derivs.* JP 2000063354.

AS-AT1R-ODN-mRNA

288144

Antisense oligodeoxynucleotide targeted to AT₁ receptor mRNA whose sequence is: 5'-TAACTGTGCCTGCCA-3'

ACTION – Antihypertensive agent, an antisense oligodeoxynucleotide targeted to angiotensin type 1 receptor mRNA. In rats with abdominal aortic banding, compound given i.v. in liposomal carriers was shown to significantly reduce mean arterial and systolic blood pressure, as well as left ventricular weight/body weight ratios. In this model, compound also induced reductions in myocardial atrial natriuretic peptide (ANP) mRNA and sarcoplasmic reticulum Ca^{2+} -ATPase.

SOURCE – University of Florida, Gainesville, FL (US).

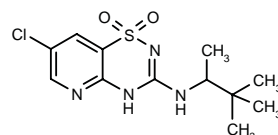
REFERENCES

1. Schmidt-Ott, K.M. et al. *Reduction of cardiac damage with AT₁-R antisense*. FASEB J 2000, 14(4): Abst 309.2.

BPDZ-83²

288062

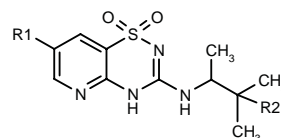
7-Chloro-3-(1,2,2-trimethylpropylamino)-4*H*-pyrido[2,3-*e*]-[1,2,4]thiadiazine 1,1-dioxide



C12 H17 Cl N4 O2 S; Mol wt: 316.8113

M.p. > 300 °C.

ACTION – ATP-sensitive potassium (K_{ATP}) channel opener with a pharmacological profile similar to that of pinacidil and diazoxide. Compound induced relaxation in rat aortic rings precontracted with 30 mM KCl ($EC_{50} = 2.3 \mu M$) and its activity was strongly reduced when the concentration of KCl increased to 80 mM ($EC_{50} = 33 \mu M$); in the presence of increasing concentrations of the K_{ATP} channel blocker glibenclamide, a concentration-dependent decrease in the myorelaxant efficiency of the compound was seen. It was selective for vascular smooth muscle tissue, being inactive on both electrically stimulated guinea pig ileum and oxytocin-contracted rat uterus. Potentially useful as an antihypertensive agent. Within this class of 3-alkylamino-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxides, the following are also included:



Compound	R1	R2	Formula
BPDZ-79 [251640]^{1,2}	H	Me	C ₁₂ H ₁₈ N ₄ O ₂ S
288060	H	H	C ₁₁ H ₁₆ N ₄ O ₂ S
288061	Cl	H	C ₁₁ H ₁₅ ClN ₄ O ₂ S

SOURCES – Université Libre de Bruxelles, Bruxelles (BE); University of Liège, Liège (BE).

REFERENCES

1. Fang, Z.-Y. et al. *Vasodilative properties of BPDZ 79, a new potassium channel opener, in isolated aorta*. Acta Pharmacol Sin 1997, 18(2): 101.

2. Pirotte, B. et al. *3-Alkylamino-4H-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxides structurally related to diazoxide and pinacidil as potassium channel openers acting on vascular smooth muscle cells: Design, synthesis, and pharmacological evaluation*. J Med Chem 2000, 43(8): 1456.

Gp91-tat

287787

L-Arginyl-L-lysyl-L-lysyl-L-arginyl-L-arginyl-L-glutaminy-L-arginyl-L-arginyl-L-arginyl-L-cysteinyl-L-seryl-L-threonyl-L-arginyl-L-isoleucyl-L-arginyl-L-arginyl-L-glutaminy-L-leucinamide

C98 H190 N50 O22 S; Mol wt: 2452.9730

ACTION – Antihypertensive agent, an inhibitor of NADPH oxidase subunits p47^{phox} and gp91^{phox} proven to decrease systolic blood pressure and inhibit peroxide anion production in angiotensin II-infused mice.

SOURCE – Henry Ford Hospital, Detroit, MI (US).

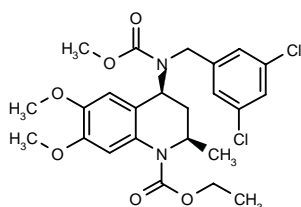
REFERENCES

1. Rey, F.E. et al. A competitive inhibitor of NADPH oxidase subunits p47^{phox} and gp91^{phox} attenuates blood pressure in angiotensin II-infused mice. *FASEB J* 2000, 14(4): Abst 113.5.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

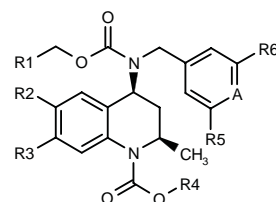
287541

4(S)-[N-(3,5-Dichlorobenzyl)-N-(methoxycarbonyl)amino]-6,7-dimethoxy-2(R)-methyl-1,2,3,4-tetrahydroquinoline-1-carboxylic acid ethyl ester



C24 H28 Cl2 N2 O6; Mol wt: 511.3992

ACTION – Cholesteryl ester transfer protein (CETP) inhibitor for use in elevating HDL cholesterol levels and lowering LDL cholesterol and triglyceride levels, for the prevention and/or treatment of atherosclerosis and associated disease states including cardiovascular disorders (angina, cardiac ischemia, myocardial infarction), complications due to cardiovascular disease therapies (reperfusion injury, angioplastic restenosis), hypertension and stroke. Other specifically claimed 4-carboxamido-2-methyl-1,2,3,4-tetrahydroquinolines are:



Compound	R1	R2	R3	R4	R5=R6	A	Formula
287542	H	OMe	OMe	Et	NO2	CH	C ₂₄ H ₂₈ N ₄ O ₁₀
287543	H	OMe	OMe	Et	Cl	N	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₆
287544	H	OMe	OMe	Et	CF3	CH	C ₂₆ H ₂₆ F ₆ N ₂ O ₆
287545	H	OMe	H	Et	CF3	CH	C ₂₅ H ₂₆ F ₆ N ₂ O ₅
287546	H	H	OMe	Et	CF3	CH	C ₂₅ H ₂₆ F ₆ N ₂ O ₅
287548	H	OMe	OMe	i-Pr	CF3	CH	C ₂₇ H ₃₀ F ₆ N ₂ O ₆
287549	Me	OMe	OMe	Et	CF3	CH	C ₂₇ H ₃₀ F ₆ N ₂ O ₆
287550	H	OMe	OMe	CH2CF3	CF3	CH	C ₂₆ H ₂₅ F ₆ N ₂ O ₆
287551	H	OMe	OMe	Pr	CF3	CH	C ₂₇ H ₃₀ F ₆ N ₂ O ₆
287552	H	OMe	OMe	t-Bu	CF3	CH	C ₂₈ H ₃₂ F ₆ N ₂ O ₆
287553	H	OCF3	H	Et	CF3	CH	C ₂₅ H ₂₃ F ₉ N ₂ O ₅

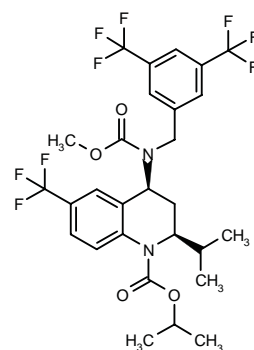
SOURCE – Pfizer.

REFERENCES

1. Goldstein, S.W. et al. (Pfizer Products Inc.) 4-Carboxyamino-2-methyl-1,2,3,4-tetrahydroquinolines as CETP inhibitors. EP 0987251.

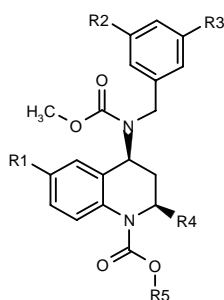
287913

4(S)-[N-[3,5-Bis(trifluoromethyl)benzyl]-N-(methoxycarbonyl)amino]-2(S)-isopropyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline-1-carboxylic acid isopropyl ester



C28 H29 F9 N2 O4; Mol wt: 628.5291

ACTION – Cholesteryl ester transfer protein (CETP) inhibitor that elevates HDL cholesterol levels and lowers LDL cholesterol and triglyceride levels, reported to be useful for the treatment of atherosclerosis and associated cardiovascular disorders. Other specifically claimed 4-carboxamido-2-substituted-1,2,3,4-tetrahydroquinolines are:



Compound	R1	R2=R3	R4	R5	Formula
287914	Cl	CF ₃	cyclopropyl	i-Pr	C ₂₇ H ₂₇ ClF ₉ N ₂ O ₄
287915	CF ₃	Cl	cyclopropyl	i-Pr	C ₂₈ H ₂₇ Cl ₂ F ₉ N ₂ O ₄
287916	CF ₃	CF ₃	cyclopropyl	t-Bu	C ₂₉ H ₂₉ F ₉ N ₂ O ₄
287917	CF ₃	CF ₃	cyclopropyl	i-Pr	C ₂₈ H ₂₇ F ₉ N ₂ O ₄
287918	CF ₃	CF ₃	cyclobutyl	i-Pr	C ₂₉ H ₂₉ F ₉ N ₂ O ₄

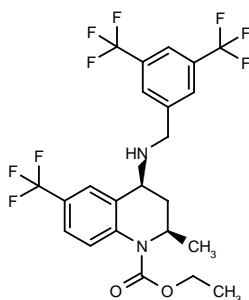
SOURCE – Pfizer.

REFERENCES

1. Deninno, M.P. et al. (Pfizer Products Inc.) 4-Carboxyamino-2-substd.-1,2,3,4-tetrahydroquinolines as CETP inhibitors. WO 0017164.

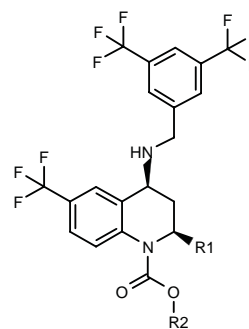
287921

4(*S*)-[3,5-Bis(trifluoromethyl)benzylamino]-2(*R*)-methyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline-1-carboxylic acid ethyl ester



C₂₃ H₂₁ F₉ N₂ O₂; Mol wt: 528.4129

ACTION – Cholesteryl ester transfer protein (CETP) inhibitor that elevates HDL cholesterol levels and lowers LDL cholesterol and triglyceride levels, reported to be useful for the treatment of atherosclerosis and associated cardiovascular disorders. Other specifically claimed 4-amino-substituted-2-substituted-1,2,3,4-tetrahydroquinolines are:



Compound	R1	R2	Formula
287922	Me	Pr	C ₂₄ H ₂₃ F ₉ N ₂ O ₂
287923	Me	i-Pr	C ₂₄ H ₂₃ F ₉ N ₂ O ₂
287924	Et	Et	C ₂₄ H ₂₃ F ₉ N ₂ O ₂
287925	Et	Pr	C ₂₅ H ₂₅ F ₉ N ₂ O ₂
287926	Et	i-Pr	C ₂₅ H ₂₅ F ₉ N ₂ O ₂
287927	cyclopropyl	Et	C ₂₅ H ₂₃ F ₉ N ₂ O ₂
287928	cyclopropyl	Pr	C ₂₆ H ₂₅ F ₉ N ₂ O ₂
287929	cyclopropyl	i-Pr	C ₂₆ H ₂₅ F ₉ N ₂ O ₂

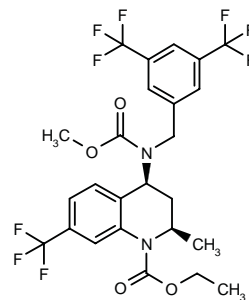
SOURCE – Pfizer.

REFERENCES

1. Deninno, M.P. et al. (Pfizer Products Inc.) 4-Amino substd.-2-substd.-1,2,3,4-tetrahydroquinolines as CETP inhibitors. WO 0017165.

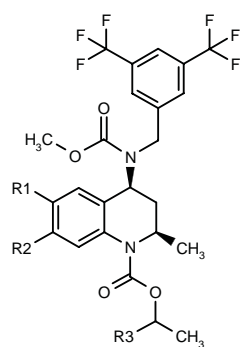
287930

4(*S*)-[*N*-[3,5-Bis(trifluoromethyl)benzyl]-*N*-(methoxycarbonyl)amino]-2(*R*)-methyl-7-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline-1-carboxylic acid ethyl ester



C₂₅ H₂₃ F₉ N₂ O₄; Mol wt: 586.4487

ACTION – Cholesteryl ester transfer protein (CETP) inhibitor that elevates HDL cholesterol levels and lowers LDL cholesterol and triglyceride levels, reported to be useful for the treatment of atherosclerosis and associated cardiovascular disorders. Other specifically claimed 4-carboxyamino-2-methyl-1,2,3,4-tetrahydroquinolines are:



Compound	R1	R2	R3	Formula
287931	H	Cl	H	C ₂₄ H ₂₃ ClF ₆ N ₂ O ₄
287932	Cl	H	H	C ₂₄ H ₂₃ ClF ₆ N ₂ O ₄
287933	Me	Me	H	C ₂₆ H ₂₈ F ₆ N ₂ O ₄
287934	Et	Et	H	C ₂₈ H ₃₂ F ₆ N ₂ O ₄
287935	Et	H	H	C ₂₆ H ₂₈ F ₆ N ₂ O ₄
287936	CF ₃	H	H	C ₂₅ H ₂₃ F ₉ N ₂ O ₄
287937	CF ₃	H	Me	C ₂₆ H ₂₅ F ₉ N ₂ O ₄

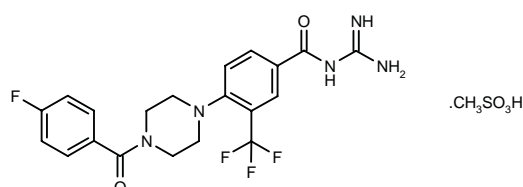
SOURCE – Pfizer.

REFERENCES

- Deninno, M.P. et al. (Pfizer Products Inc.) 4-Carboxyamino-2-methyl-1,2,3,4-tetrahydroquinolines as CETP inhibitors. WO 0017166.

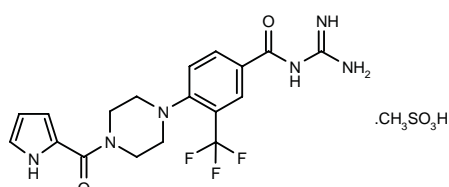
288007

N-[4-[4-(4-Fluorobenzoyl)piperazin-1-yl]-3-(trifluoromethyl)benzoyl]guanidine methanesulfonate



C₂₀ H₁₉ F₄ N₅ O₂ . C H₄ O₃ S; Mol wt: 533.5007

ACTION – Na⁺/H⁺ exchange inhibitor (IC₅₀ = 0.039 μM in human colon cancer cells) for the treatment of ischemia. It showed a good oral bioavailability and a long half-life following i.v. or oral administration in rats. Another specifically claimed benzoylguanidine derivative is:



288008: C₁₈ H₁₉ F₃ N₆ O₂ . C H₄ O₃ S

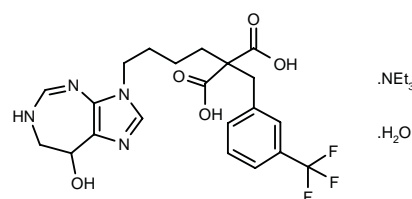
SOURCE – Boehringer Ingelheim.

REFERENCES

- Roos, O. et al. (Boehringer Ingelheim Pharma KG) Benzoylguanidine derivs. with advantageous properties, method for producing them and their use in the production of medicaments. DE 19843489, WO 0017176.

288065

2-[4-[8-Hydroxy-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]-diazepin-3-yl]butyl]-2-[3-(trifluoromethyl)benzyl]malonic acid triethylamine salt hydrate



C₂₁ H₂₃ F₃ N₄ O₅ . C₆ H₁₅ N . H₂O; Mol wt: 587.6360

M.p. 122-3 °C.

ACTION – Potent AMP deaminase inhibitor (K_i = 0.029 μM) with high selectivity over dopamine deaminase (K_i > 7.5 μM), potentially useful for the treatment of ischemia.

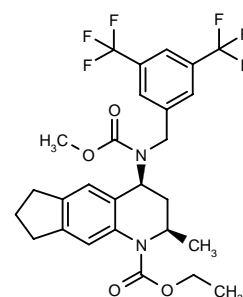
SOURCE – Metabasis.

REFERENCES

- Bookser, B.C. et al. AMP deaminase inhibitors. 4. Further N3-substituted coformycin aglycon analogues: N3-alkylmalonates as ribose 5'-monophosphate mimetics. J Med Chem 2000, 43(8): 1519.

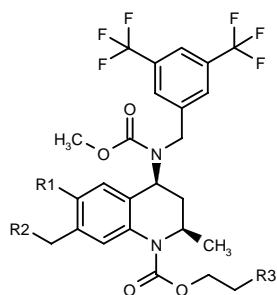
288221

4(*S*)-[*N*-[3,5-Bis(trifluoromethyl)benzyl]-*N*-(methoxycarbonyl)amino]-2(*R*)-methyl-2,3,4,6,7,8-hexahydro-1*H*-cyclopenta[*g*]quinoline-1-carboxylic acid ethyl ester



C₂₇ H₂₈ F₆ N₂ O₄; Mol wt: 558.5162

ACTION – Cholesteryl ester transfer protein (CETP) inhibitor for use in elevating HDL cholesterol levels and lowering LDL cholesterol and triglyceride levels. This compound is potentially useful for the prevention and/or treatment of atherosclerosis and associated disease states including cardiovascular disorders (angina, cardiac ischemia, myocardial infarction), complications due to cardiovascular disease therapies (reperfusion injury, angioplastic restenosis), hypertension, stroke, etc. Other specifically claimed annelated 4-carboxamido-2-methyl-1,2,3,4-tetrahydroquinolines are:



Compound	R1,R2	R3	Formula
288225	-CH ₂ S-	H	C ₂₆ H ₂₆ F ₆ N ₂ O ₄ S
288226	-OCH ₂ -	H	C ₂₆ H ₂₆ F ₆ N ₂ O ₅
288227	-CH ₂ O-	H	C ₂₆ H ₂₆ F ₆ N ₂ O ₅
288228	-(CH ₂) ₃ -	Me	C ₂₉ H ₃₂ F ₆ N ₂ O ₄

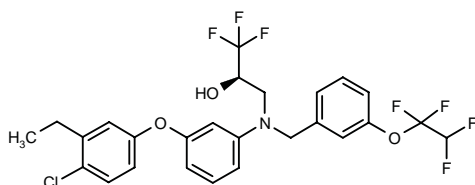
SOURCE – Pfizer.

REFERENCES

- Deninno, M.P. et al. (Pfizer Products Inc.) *Annelated 4-carboxy-amino-2-methyl-1,2,3,4-tetrahydroquinolines as CETP inhibitors*. EP 0992496, JP 2000095764.

288257

3-[N-[3-(4-Chloro-3-ethylphenoxy)phenyl]-N-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino]-1,1,1-trifluoropropan-2-ol



C26 H23 Cl F7 N O3; Mol wt: 565.9107

ACTION – Agent for the treatment or prevention of coronary artery disease, cerebral vascular accidents (CVA) and dyslipidemia, an inhibitor of cholesteryl ester transfer protein (CETP), as demonstrated *in vitro* (IC₅₀ = 0.0008 and 0.049 μM, respectively, against recombinant enzyme and enzyme from human plasma) and *ex vivo* in hamsters (35% inhibition at 10 mg/kg p.o.) and hCETP-transfected mice (40% inhibition at 60 mg/kg p.o.). When tested in a chronic assay in cholesterol-fed hamsters at 30 mg/kg/day q.d. p.o. x 5 days, it produced 12 and 22% reductions and a 12% increase in LDL, VLDL and HDL cholesterol levels, respectively. A representative compound from a series of (R)-chiral halogenated 1-substituted aminoalkanols.

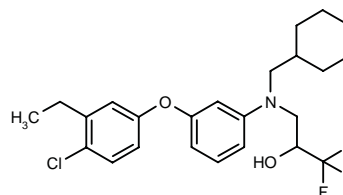
SOURCE – Pharmacia.

REFERENCES

- Sikorski, J.A. et al. (Monsanto Co.) *(R)-Chiral halogenated 1-substd.amino-(n+1)-alkanols useful for inhibiting cholesteryl ester transfer protein activity*. WO 0018724.

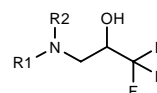
288277

3-[N-[3-(4-Chloro-3-ethylphenoxy)phenyl]-N-(cyclohexylmethyl)amino]-1,1,1-trifluoropropan-2-ol



C24 H29 Cl F3 N O2; Mol wt: 455.9451

ACTION – Agent for the treatment or prevention of coronary artery disease, cerebral vascular accidents (CVA) and dyslipidemia, an inhibitor of cholesteryl ester transfer protein (CETP; IC₅₀ = 11 μM using human enzyme). Other compounds within this series of substituted N-aliphatic-N-aromatic tertiary-heteroalkylamines include the following:



Compound	R1	R2	Formula
288278	4-Me-cyclohexyl	3-CF ₃ -PhCH ₂	C ₁₈ H ₂₃ F ₆ NO
288280	3-(CF ₃ O)-PhCH ₂	cyclopropyl	C ₁₄ H ₁₅ F ₆ NO ₂
288281	CH ₂ CH=CHC ₅ H ₁₁	3-CF ₃ O-Ph	C ₁₈ H ₂₃ F ₆ NO ₂
288283	3-CF ₃ -PhCH ₂	CH ₂ CH(OH)CF ₃	C ₁₄ H ₁₄ F ₉ NO ₂

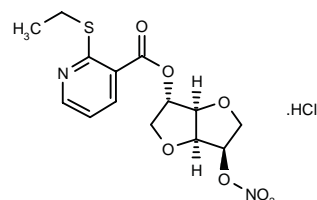
SOURCE – Pharmacia.

REFERENCES

- Sikorski, J.A. et al. (Monsanto Co.) *Substd. N-aliphatic-N-aromatic tertiary-heteroalkylamines useful for inhibiting cholesteryl ester transfer protein activity*. WO 0018723.

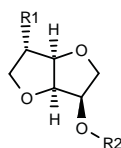
288445

2-(Ethylsulfanyl)pyridine-3-carboxylic acid (3S,3aS, 6R,6aS)-6-(nitrooxy)perhydrofuro[3,2-b]furan-3-yl ester hydrochloride



C14 H16 N2 O7 S . HCl; Mol wt: 392.8143

ACTION – A representative compound from a series of isosorbide mononitrate derivatives with vasodilating activity and reduced potential for tolerance development. Compound was found to be more potent than isosorbide mononitrate in relaxing rat aortic rings precontracted with norepinephrine (EC₅₀ = 0.13 μM vs. 0.92 μM for isosorbide mononitrate) while exhibiting reduced tolerance following administration of 10 mg/kg/day s.c. x 3 days to rats. Other specifically claimed compounds are:



Compound	R1	R2	Formula
288446	ONO2	2-EtS-3-Pyr-CO	C ₁₄ H ₁₇ ClN ₂ O ₇ S
288447	2-SH-3-Pyr-COO	NO2	C ₁₂ H ₁₂ N ₂ O ₇ S
288448	ONO2	2-SH-3-Pyr-CO	C ₁₂ H ₁₂ N ₂ O ₇ S
288450	SAC	NO2	C ₈ H ₁₁ NO ₆ S

SOURCE – Lacer.

REFERENCES

1. Repolles Moliner, J. et al. (Lacer SA) *Derivs. of isosorbid mononitrate, utilization as vasodilator agents with reduced tolerance*. ES 2142773, WO 0020420.

AdRasN17

287876

Replication-deficient adenovirus encoding the RasN17 gene, a gene which encodes a dominant negative mutant of Ras

ACTION – Recombinant replication-deficient adenovirus encoding the RasN17 gene, a dominant negative mutant of Ras, with potential as gene therapy for the prevention of restenosis induced by balloon angioplasty. Compound was found to inhibit the proliferation of both cultured vascular smooth muscle cells and VSMCs derived from common carotid arteries of rats subjected to balloon angioplasty; it reduced ERK (extracellular signal-regulated kinase) activity and neointima formation, which were markedly increased after balloon angioplasty in rats.

SOURCE – University of California, San Diego, La Jolla, CA (US).

REFERENCES

1. Jin, G. et al. *Role of Ras signaling pathway in neointima formation in rat arteries*. FASEB J 2000, 14(4): Abst 307.6.

15B8 MAb

288663

Monoclonal antibody to Tie2 receptor

ACTION – Tie2 receptor agonist antibody useful for enhancing angiogenesis, with high affinity for Tie2 in an immunoassay ($K_D = 0.24$ nM). It was shown to stimulate angiogenesis *in vivo* in a matrigel vascularization model in mice at a concentration of 100 µg/ml, as well as to promote enhanced survival of human umbilical vein endothelial cells (HUVEC) over a period of 48 h at a concentration of 50 µg/ml. Claimed for the treatment of ischemic diseases such as myocardial infarction and stroke, as well as vascular diseases such as diabetes. Another specifically claimed agonist antibody is:

Monoclonal antibody to Tie2 receptor

13H10 MAb [288666]

SOURCE – SmithKline Beecham.

REFERENCES

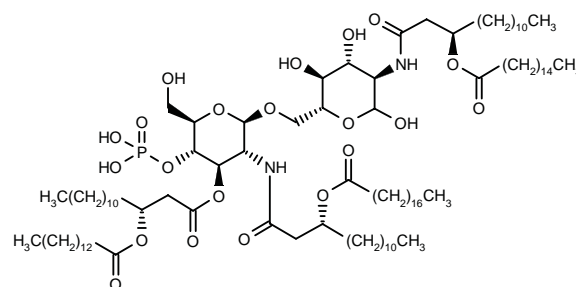
1. Holmes, S.D. et al. (SmithKline Beecham Corp.; SmithKline Beecham plc) *Tie2 agonist antibodies*. WO 0018804.

RC-552

286771

2-Deoxy-6-O-[2-deoxy-4-O-phosphono-3-O-[3(R)-(tetradecanoyloxy)tetradecanoyl]-2-[3(R)-(octadecanoyloxy)-tetradecanamido]-β-D-glucopyranosyl]-2-[3(R)-(hexadecanoyloxy)tetradecanamido]-D-glucopyranose

RC-552C



C102 H193 N2 O21 P; Mol wt: 1814.6140

ACTION – Synthetic glycolipid with cardioprotective activity and no immunostimulating activity, unlike the glycolipid monophosphoryl A and lipopolysaccharide. In a model of myocardial infarction induced by occlusion of the left anterior descending coronary artery followed by reperfusion in anesthetized dogs with a left thoracotomy, compound (29 µg/kg by i.v. bolus 10 min before occlusion, followed by continuous infusion of 3.3 µg/kg/h over 3 h) significantly reduced infarct size at 4 days after ischemia/reperfusion, as well as the average heart rate during occlusion. In other myocardial infarction models in mice, dogs and pigs, it proved to be effective even when administration was begun 3 h before ischemia, and it has shown no prodysrhythmic effects, no effect on collateral blood flow or hemodynamics and no pyrogenicity. Potentially useful for the treatment of myocardial ischemia.

SOURCE – Corixa.

REFERENCES

1. Elliott, G.T. et al. (Corixa Corp.) *Phosphoglycolipid and methods for its use*. WO 0011010.
2. Elliott, G. et al. *Sustained acute cardioprotection by the novel glycolipid, RC-552, in a canine infarct model*. 2nd Int Congr Coron Artery Dis (Oct 18-21, Florence) 1998, Abst 523.
3. Elliott, G.T. et al. *Low-dose continuous infusion of the synthetic glycolipid RC-552 provides sustained cardioprotection against infarction in dogs*. Eur Heart J 1999, 20(Suppl.): Abst P1036.
4. Gross, G. et al. *The novel glycolipid, RC-552, demonstrates acute and durable cardioprotection against infarction in dogs without residual pyrogenicity*. 2nd Int Congr Coron Artery Dis (Oct 18-21, Florence) 1998, Abst 351.
5. Krolkowski, J.G. and Bosnjak, Z.J. *The synthetic glycolipid, RC-552, produces long term reduction of myocardial infarct size in dogs*. FASEB J 2000, 14(4): Abst 310.6.

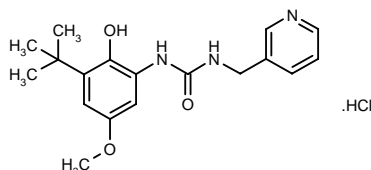
6. Krolkowski, J.G. et al. *A new synthetic analogue of monophosphoryl lipid A, RC-552 produces cardioprotection without prodysrhythmic effects in conscious dogs.* FASEB J 1999, 13(5, Part 2): Abst 598.22.

7. Xi, L. et al. *Delayed anti-infarct protection induced by a novel glycolipid - RC552C against myocardial ischemia/reperfusion injury in mice.* FASEB J 1999, 13(5, Part 2): Abst 598.3.

T-0162

288506

N-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-*N'*-(3-pyridylmethyl)urea hydrochloride



C18 H23 N3 O3 . HCl; Mol wt: 365.8586

M.p. 200-2 °C.

ACTION – Low-molecular-weight free radical scavenger proven to scavenge superoxide anions (1-10 $\mu\text{mol/l}$) *in vitro* and hydroxyl radicals both *in vitro* (10-100 $\mu\text{mol/l}$) and *in vivo* in a rabbit model of myocardial infarction. In Japanese white male rabbits subjected to 30 min of coronary occlusion and 48 h of reperfusion, compound (infused i.v. at 400 $\mu\text{g/kg/min}$ for 220 min) as pre- or posttreatment was found to reduce infarct size (measured as a percentage of the area at risk) from 44.7% in controls to 24.8% with pretreatment and to 30.5% with post-treatment. No significant changes in hemodynamic parameters were seen throughout the experimental period. Potentially useful for the treatment of acute myocardial infarction.

SOURCE – Tanabe Seiyaku.

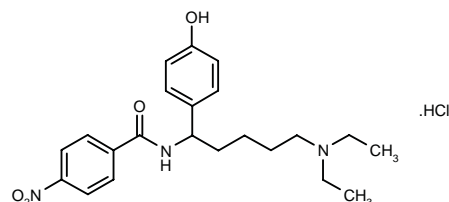
REFERENCES

1. Suzuki, T. et al. (Tanabe Seiyaku Co., Ltd.) *Medicinal compsns.* JP 1999139969.
2. Suzuki, T. et al. (Tanabe Seiyaku Co., Ltd.) *Phenol-derivs. having pharmaceutical activity and process for preparing the same.* EP 0790240, JP 1998195037, US 5849732.
3. Nakao, K. et al. *Quantitative structure-activity analyses of novel hydroxyphenylurea derivatives as antioxidants.* Bioorg Med Chem 1998, 6(6): 849.
4. Yamashita, K. et al. *T-0162, a novel free radical scavenger, reduces myocardial infarct size in rabbits.* Clin Exp Pharmacol Physiol 2000, 27(3): 172.

ANTIARRHYTHMIC DRUGS

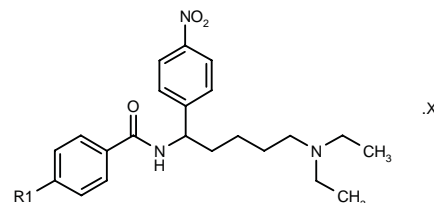
287253

(\pm)-*N*-[5-(Diethylamino)-1-(4-hydroxyphenyl)pentyl]-4-nitro-benzamide hydrochloride



C22 H29 N3 O4 . HCl; Mol wt: 435.9490

ACTION – Antiarrhythmic agent, the principal metabolite of nibentan⁺ with improved antifibrillatory activity and a longer duration of action (up to 5 h vs. 1-1.5 h) in cats. Other nibentan analogues are:



Compound	R1	X	Formula
287251	H		C ₂₂ H ₂₉ N ₃ O ₃
287252	NO ₂	HCl	C ₂₂ H ₂₈ N ₄ O ₅ .HCl

SOURCE – Center for Chemistry of Drugs, Moscow (RU).

REFERENCES

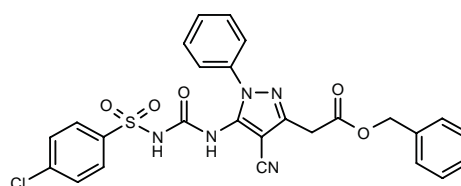
1. Davydova, N.K. et al. *Synthesis and antifibrillatory activity of nibentan and its analogues.* Eur J Med Chem 2000, 35(2): 205.

*Drug Data Rep 1996, 018(08): 0712.

HEART FAILURE THERAPY

287320

2-[5-[3-(4-Chlorophenylsulfonyl)ureido]-4-cyano-1-phenyl-1*H*-pyrazol-3-yl]acetic acid benzyl ester



C26 H20 Cl N5 O5 S; Mol wt: 549.9930

ACTION – A representative compound from a series of sulfonylureidopyrazoles with endothelin-converting enzyme (ECE)-inhibitory activity, as demonstrated against rat lung enzyme ($IC_{50} = 0.058 \mu M$).

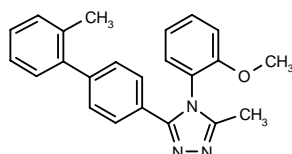
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Hasegawa, H. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Sulfonyl ureidopyrazole derivs.* JP 2000053649.

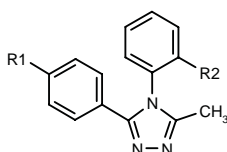
287509

4-(2-Methoxyphenyl)-3-methyl-5-(2'-methylbiphenyl-4-yl)-4*H*-1,2,4-triazole

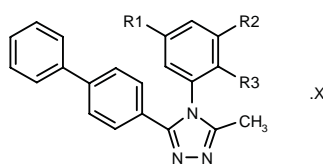


C₂₃H₂₁N₃O; Mol wt: 355.4389

ACTION – Vasopressin V₁ receptor antagonist expected to be useful for the treatment of disorders such as heart failure and hypertension. A representative compound from a series of triazole derivatives, wherein the following are also included:



Compound	R1	R2	Formula
287511	OPh	OMe	C ₂₂ H ₁₉ N ₃ O ₂
287512	2-Et-1-imidazolyl	OCH ₂ Ph	C ₂₇ H ₂₅ N ₅ O



Compound	R1	R2	R3	X	Formula
287513	CN	H	4-(4-Me-1-Piz-CO)-PhCH ₂ O		C ₃₅ H ₃₂ N ₆ O ₂
287515	H	H	I		C ₂₁ H ₁₆ N ₃
287516	H	H	4-Me-1-Piz		C ₂₆ H ₂₇ N ₅
287517	H	H	4-Me-1-Piz-(CH ₂) ₃ -NHCOCH ₂ O		C ₃₁ H ₃₆ N ₆ O ₂
287518	H	H	1-pyrrolidinyl-CH ₂ CH ₂ NH(CH ₂) ₆ O	trifumarate	C ₃₃ H ₄₁ N ₅ O ₃
287519	H	H	4-[4-[4-(1-Pip)-1-Pip-CO]-PhCO]-PhCH ₂ O		C ₄₆ H ₄₅ N ₅ O ₃
287520	H	OH	H		C ₂₁ H ₁₇ N ₃ O

SOURCE – Yamanouchi.

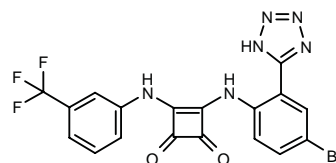
REFERENCES

1. Suzuki, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel triazole derivs.* JP 2000063363.

MISCELLANEOUS CARDIOVASCULAR DRUGS

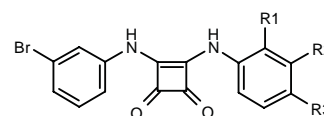
288465

3-[4-Bromo-2-(1*H*-tetrazol-5-yl)phenylamino]-4-[3-(trifluoromethyl)phenylamino]-3-cyclobutene-1,2-dione



C₁₈H₁₀BrF₃N₆O₂; Mol wt: 479.2150

ACTION – Potent blocker of chloride channels in normal and sickle cell erythrocytes, expected to be of use for the treatment of sickle cell anemia, brain edema following ischemia or tumors, diarrhea, hypertension, osteoporosis, bone-metastazing cancers, ulcers, allergic or inflammatory conditions and glaucoma. Other diaminocyclobutene-3,4-dione derivatives are:



Compound	R1	R2	R3	Formula
288466	5-tetrazolyl	H	Br	C ₁₇ H ₁₀ Br ₂ N ₆ O ₂
288467	5-tetrazolyl	H	4-[N(Me)2SO2]-Ph	C ₂₅ H ₂₀ BrN ₇ O ₄ S
288468	H	5-tetrazolyl	Ph	C ₂₃ H ₁₅ BrN ₆ O ₂

SOURCE – NeuroSearch.

REFERENCES

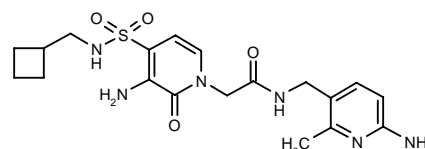
1. Dahl, B.H. and Christophersen, P. (NeuroSearch A/S) *Diaminocyclobutene-3,4-dione derivs., their preparation and use.* WO 0020378.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

288172

2-[3-Amino-4-(*N*-cyclobutylmethylsulfamoyl)-2-oxo-1,2-dihydropyridin-1-yl]-*N*-(6-amino-2-methylpyridin-3-ylmethyl)acetamide



C₁₉H₂₆N₆O₄S; Mol wt: 434.5184

ACTION – A representative compound from a series of sulfonylureidopyrazoles with endothelin-converting enzyme (ECE)-inhibitory activity, as demonstrated against rat lung enzyme (IC₅₀ = 0.058 μM).

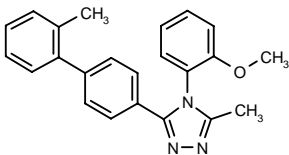
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

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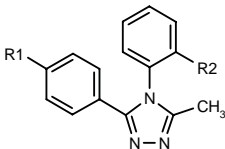
287509

4-(2-Methoxyphenyl)-3-methyl-5-(2'-methylbiphenyl-4-yl)-4*H*-1,2,4-triazole

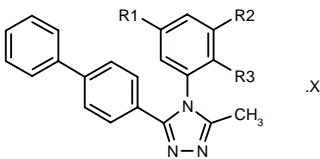


C23 H21 N3 O; Mol wt: 355.4389

ACTION – Vasopressin V₁ receptor antagonist expected to be useful for the treatment of disorders such as heart failure and hypertension. A representative compound from a series of triazole derivatives, wherein the following are also included:



Compound	R1	R2	Formula
287511	OPh	OMe	C ₂₂ H ₁₉ N ₃ O ₂
287512	2-Et-1-imidazolyl	OCH2Ph	C ₂₇ H ₂₅ N ₅ O



Compound	R1	R2	R3	X	Formula
287513	CN	H	4-(4-Me-1-Piz-CO)-PhCH2O		C ₃₅ H ₃₂ N ₆ O ₂
287515	H	H	I		C ₂₁ H ₁₆ IN ₃
287516	H	H	4-Me-1-Piz		C ₂₈ H ₂₇ N ₅
287517	H	H	4-Me-1-Piz-(CH2)3-NHCOCH2O		C ₃₁ H ₃₆ N ₆ O ₂
287518	H	H	1-pyrrolidinyl-CH2CH2NH(CH2)6O	trifumarate	C ₃₃ H ₄₁ N ₅ O .3C ₄ H ₄ O ₄
287519	H	H	4-[4-(1-Pip)-1-Pip-CO]-PhCO]-PhCH2O		C ₄₆ H ₄₅ N ₅ O ₃
287520	H	OH	H		C ₂₁ H ₁₇ N ₃ O

SOURCE – Yamanouchi.

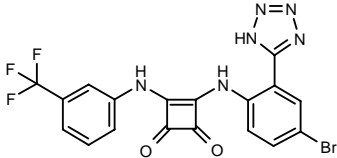
REFERENCES

1. Suzuki, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel triazole derivs.* JP 2000063363.

MISCELLANEOUS
CARDIOVASCULAR DRUGS

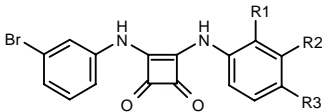
288465

3-[4-Bromo-2-(1*H*-tetrazol-5-yl)phenylamino]-4-[3-(trifluoromethyl)phenylamino]-3-cyclobutene-1,2-dione



C18 H10 Br F3 N6 O2; Mol wt: 479.2150

ACTION – Potent blocker of chloride channels in normal and sickle cell erythrocytes, expected to be of use for the treatment of sickle cell anemia, brain edema following ischemia or tumors, diarrhea, hypertension, osteoporosis, bone-metastazing cancers, ulcers, allergic or inflammatory conditions and glaucoma. Other diaminocyclobutene-3,4-dione derivatives are:



Compound	R1	R2	R3	Formula
288466	5-tetrazolyl	H	Br	C ₁₇ H ₁₀ Br ₂ N ₆ O ₂
288467	5-tetrazolyl	H	4-[N(Me)2SO2]-Ph	C ₂₅ H ₂₀ BrN ₇ O ₄ S
288468	H	5-tetrazolyl	Ph	C ₂₃ H ₁₅ BrN ₆ O ₂

SOURCE – NeuroSearch.

REFERENCES

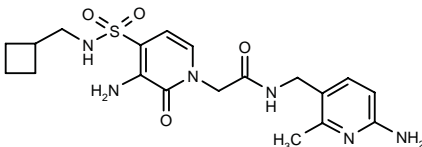
1. Dahl, B.H. and Christophersen, P. (NeuroSearch A/S) *Diaminocyclobutene-3,4-dione derivs., their preparation and use.* WO 0020378.

AGENTS AFFECTING BLOOD
COAGULATION

ANTICOAGULANTS

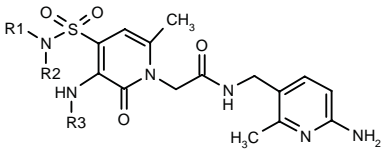
288172

2-[3-Amino-4-(*N*-cyclobutylmethylsulfamoyl)-2-oxo-1,2-dihydropyridin-1-yl]-*N*-(6-amino-2-methylpyridin-3-ylmethyl)acetamide



C19 H26 N6 O4 S; Mol wt: 434.5184

ACTION – Thrombin inhibitor for the treatment and prevention of thrombotic conditions, particularly coronary artery and cerebrovascular disease. It is reported to be selective with respect to human trypsin. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
288173	cyclobutyl-CH2	-CH2-		C ₂₁ H ₂₈ N ₆ O ₄ S
288174	cyclobutyl	H	H	C ₁₉ H ₂₆ N ₆ O ₄ S
288175	-(CH2)4-		H	C ₁₉ H ₂₆ N ₆ O ₄ S

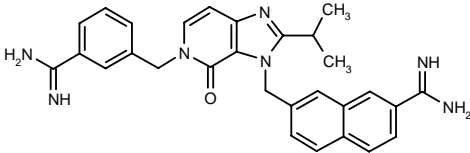
SOURCE – Merck & Co.

REFERENCES

1. Sanderson, P.E. and Cutrona, K. (Merck & Co., Inc.) *Thrombin inhibitors*. WO 0018762.

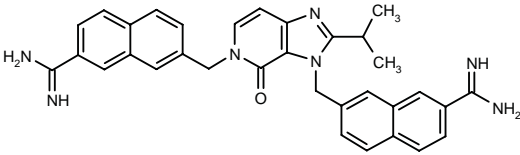
288435

7-[5-(3-Amidinobenzyl)-2-isopropyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]pyridin-3-ylmethyl]naphthalene-2-carbox-amidine



C29 H29 N7 O; Mol wt: 491.5961

ACTION – Factor Xa inhibitor for use in the treatment of thromboembolic diseases such as thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, restenosis following angioplasty and intermittent claudication. Another specifically claimed imidazo[4,5-c]-pyridin-4-one derivative is:



288436: C33 H31 N7 O

SOURCE – Merck KGaA.

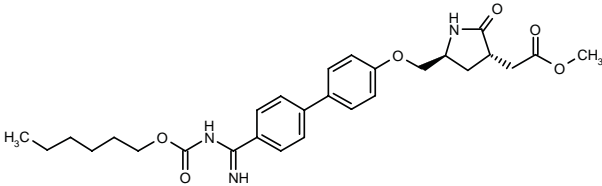
REFERENCES

1. Gante, J. et al. (Merck Patent GmbH) *Imidazo[4,5-c]-pyridine-4-one derivs. with factor Xa inhibiting effect*. DE 19845153, WO 0020416.

ANTIPLATELET THERAPY

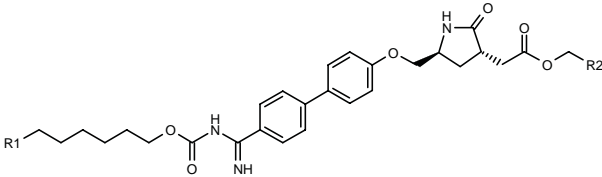
288348

2-[5(S)-[4'-[N¹-(Hexyloxycarbonyl)amidino]biphenyl-4-yloxymethyl]-2-oxopyrrolidin-3(S)-yl]acetic acid methyl ester



C28 H35 N3 O6; Mol wt: 509.5995

ACTION – Antithrombotic agent and platelet aggregation inhibitor, a representative compound from a series of disubstituted pyrrolidinone derivatives. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
288349	Et	H	C ₃₀ H ₃₉ N ₃ O ₆
288350	Bu	H	C ₃₂ H ₄₃ N ₃ O ₆
288351	C6H13	H	C ₃₄ H ₄₇ N ₃ O ₆
288353	C8H17	H	C ₃₆ H ₅₁ N ₃ O ₆
288354	C10H21	H	C ₃₈ H ₅₅ N ₃ O ₆
288356	H	Me	C ₂₉ H ₃₇ N ₃ O ₆
288357	Et	Me	C ₃₁ H ₄₁ N ₃ O ₆
288358	Bu	Me	C ₃₃ H ₄₅ N ₃ O ₆
288359	C6H13	Me	C ₃₅ H ₄₉ N ₃ O ₆
288360	C8H17	Me	C ₃₇ H ₅₃ N ₃ O ₆
288361	C10H21	Me	C ₃₉ H ₅₇ N ₃ O ₆

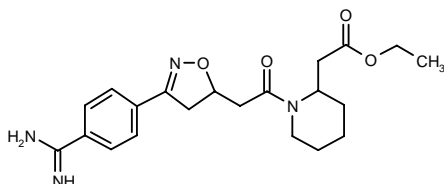
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Himmelsbach, F. et al. (Boehringer Ingelheim Pharma KG) *Disubst. pyrrolidinones, medicaments containing these cpds., their use and the production thereof*. WO 0018732.

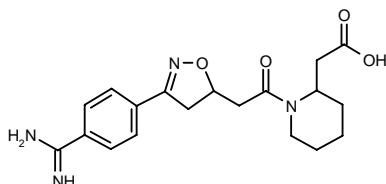
288814

2-[1-[2-[3-(4-Amidinophenyl)-4,5-dihydroisoxazol-5-yl]-acetyl]piperidin-2-yl]acetic acid ethyl ester



C21 H28 N4 O4; Mol wt: 400.4762

ACTION – Antiplatelet agent, the ethyl ester of a ring-constrained analogue of the gpIIb/IIIa receptor antagonist XR-299 proven to inhibit *ex vivo* platelet aggregation in dogs by 100% at 3 h after a dose 1 mg/kg i.v. The free acid exhibited similar *in vitro* antiplatelet activity to the parent compound XR-299 (IC_{50} = 0.28 and 0.24 μ M, respectively). The preferred isomer of the free acid is:



SV-873 [228051]*: C19 H24 N4 O4: Isomer C

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Wityak, J. et al. (DuPont Pharmaceuticals Co.) *Novel isoxazoline and isoxazole fibrinogen receptor antagonists*. EP 0730590, EP 0832076, JP 1997505590, JP 1999504651, US 5849736, WO 9514683, WO 9638426.

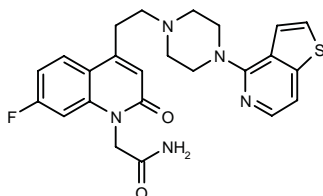
2. Sielecki, T.M. et al. *Ring constrained analogues of β -alanine-containing GPIIb/IIIa receptor antagonists*. Bioorg Med Chem Lett 2000, 10(5): 449.

*Identified compound **228051** (see **226267**) Drug Data Rep 1995, 017(11): 1007.

SL-65.0472

288000

2-[7-Fluoro-2-oxo-4-[2-[4-(thieno[3,2-*c*]pyridin-4-yl)-piperazin-1-yl]ethyl]1,2-dihydroquinolin-1-yl]acetamide



C24 H24 F N5 O2 S; Mol wt: 465.5506

ACTION – 5-HT receptor antagonist proven to inhibit 5-HT-induced platelet shape change (IC_{50} = 34.9, 68.9 and 226 nM, respectively, in rat, rabbit and human platelet-rich plasma). Compound was also seen to inhibit platelet aggregation induced by 5-HT in the presence of ATP and collagen (IC_{50} = 49 and 48 nM, respectively). In the arteriovenous shunt model in rats and rabbits, dose-dependent decreases in thrombus weight (from 164 mg to 84 mg after 1 mg/kg i.v. in rats and from 36 mg to 21 mg after 10 mg/kg p.o. in rabbits) were obtained. In a model of electrically induced femoral arterial thrombus formation in rabbits, compound dose-dependently increased the delay to femoral occlusion, from 17.5 min to 61.6 min at a dose of 20 mg/kg p.o. Moreover, it inhibited vasoconstriction mediated by 5-HT_{1B} (ID_{50} = 10.8 μ g/kg i.v. against sumatriptan-induced reduction in saphenous vein diameter in dogs) and 5-HT_{2A} (ID_{50} = 1.38 and 31.1 μ g/kg i.v. and p.o., respectively, against 5-HT-induced increase in mean arterial blood pressure in rats). In an anesthetized dog coronary thrombosis model, compound decreased cyclic variations in blood flow and it increased minimal coronary flow from 1.2 ml/min to 31.8 ml/min after a dose of 30 μ g/kg i.v.

SOURCE – Sanofi-Synthelabo.

REFERENCES

1. Mc Cort, G. et al. (Sanofi-Synthelabo) *Quinolein-2(1H)-one derivs. as serotonin antagonists*. EP 0850235, FR 2738822, FR 2739100, JP 1999514982, US 5958924, WO 9710238.

2. Berry, C.N. et al. *Antiplatelet and oral antithrombotic activity of SL 65.0472*. Br J Pharmacol 2000, 129(Suppl.): Abstr 57P.

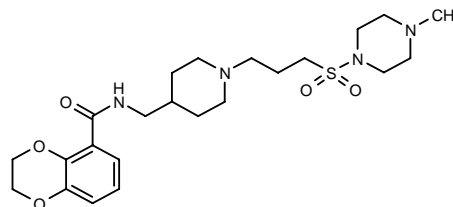
3. O'Connor, S.E. et al. *5-HT_{1B} and 5-HT_{2A} receptor antagonist properties of SL 65.0472 in vivo*. Br J Pharmacol 2000, 129(Suppl.): Abstr 58P.

4. *Sanofi-Synthelabo presents overhauled R&D portfolio to financial analysis*. DailyDrugNews.com (Daily Essentials) 2000, March 21.

RENAL-UROLOGIC DRUGS**TREATMENT OF URINARY INCONTINENCE**

287569

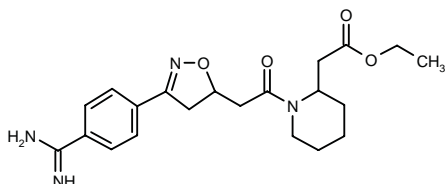
N-[1-[3-(4-Methylpiperazin-1-ylsulfonyl)propyl]piperidin-4-ylmethyl]-2,3-dihydro-1,4-benzodioxin-5-carboxamide



C23 H36 N4 O5 S; Mol wt: 480.6264

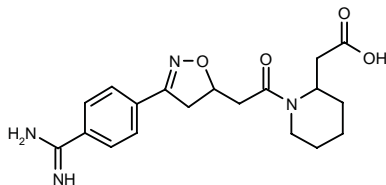
288814

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C21 H28 N4 O4; Mol wt: 400.4762

ACTION – Antiplatelet agent, the ethyl ester of a ring-constrained analogue of the gpIIb/IIIa receptor antagonist XR-299 proven to inhibit *ex vivo* platelet aggregation in dogs by 100% at 3 h after a dose 1 mg/kg i.v. The free acid exhibited similar *in vitro* antiplatelet activity to the parent compound XR-299 (IC_{50} = 0.28 and 0.24 μ M, respectively). The preferred isomer of the free acid is:



SV-873 [228051]*: C19 H24 N4 O4: Isomer C

SOURCE – DuPont Pharmaceuticals.

REFERENCES

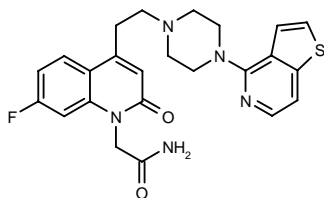
1. Wityak, J. et al. (DuPont Pharmaceuticals Co.) *Novel isoxazoline and isoxazole fibrinogen receptor antagonists*. EP 0730590, EP 0832076, JP 1997505590, JP 1999504651, US 5849736, WO 9514683, WO 9638426.

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*Identified compound **228051** (see **226267**) Drug Data Rep 1995, 017(11): 1007.

SL-65.0472**288000**

2-[7-Fluoro-2-oxo-4-[2-[4-(thieno[3,2-*c*]pyridin-4-yl)-piperazin-1-yl]ethyl]1,2-dihydroquinolin-1-yl]acetamide



C24 H24 F N5 O2 S; Mol wt: 465.5506

ACTION – 5-HT receptor antagonist proven to inhibit 5-HT-induced platelet shape change (IC_{50} = 34.9, 68.9 and 226 nM, respectively, in rat, rabbit and human platelet-rich plasma). Compound was also seen to inhibit platelet aggregation induced by 5-HT in the presence of ATP and collagen (IC_{50} = 49 and 48 nM, respectively). In the arteriovenous shunt model in rats and rabbits, dose-dependent decreases in thrombus weight (from 164 mg to 84 mg after 1 mg/kg i.v. in rats and from 36 mg to 21 mg after 10 mg/kg p.o. in rabbits) were obtained. In a model of electrically induced femoral arterial thrombus formation in rabbits, compound dose-dependently increased the delay to femoral occlusion, from 17.5 min to 61.6 min at a dose of 20 mg/kg p.o. Moreover, it inhibited vasoconstriction mediated by 5-HT_{1B} (ID_{50} = 10.8 μ g/kg i.v. against sumatriptan-induced reduction in saphenous vein diameter in dogs) and 5-HT_{2A} (ID_{50} = 1.38 and 31.1 μ g/kg i.v. and p.o., respectively, against 5-HT-induced increase in mean arterial blood pressure in rats). In an anesthetized dog coronary thrombosis model, compound decreased cyclic variations in blood flow and it increased minimal coronary flow from 1.2 ml/min to 31.8 ml/min after a dose of 30 μ g/kg i.v.

SOURCE – Sanofi-Synthelabo.

REFERENCES

1. Mc Cort, G. et al. (Sanofi-Synthelabo) *Quinolein-2(1H)-one derivs. as serotonin antagonists*. EP 0850235, FR 2738822, FR 2739100, JP 1999514982, US 5958924, WO 9710238.

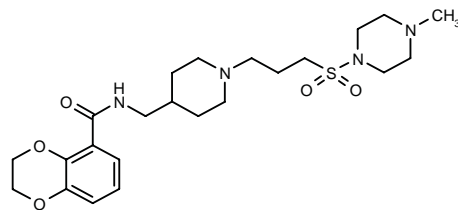
2. Berry, C.N. et al. *Antiplatelet and oral antithrombotic activity of SL 65.0472*. Br J Pharmacol 2000, 129(Suppl.): Abstr 57P.

3. O'Connor, S.E. et al. *5-HT_{1B} and 5-HT_{2A} receptor antagonist properties of SL 65.0472 in vivo*. Br J Pharmacol 2000, 129(Suppl.): Abstr 58P.

4. *Sanofi-Synthelabo presents overhauled R&D portfolio to financial analysis*. DailyDrugNews.com (Daily Essentials) 2000, March 21.

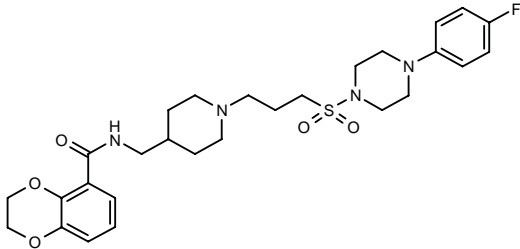
RENAL-UROLOGIC DRUGS**TREATMENT OF URINARY INCONTINENCE****287569**

N-[1-[3-(4-Methylpiperazin-1-ylsulfonyl)propyl]piperidin-4-ylmethyl]-2,3-dihydro-1,4-benzodioxin-5-carboxamide



C23 H36 N4 O5 S; Mol wt: 480.6264

ACTION – 5-HT₄ receptor antagonist found to inhibit relaxation responses to 5-HT in isolated rat esophageal muscularis mucosae, while no agonist effect was observed. It also inhibited 5-HT-induced tachycardia in anesthetized and vagotomized micropigs. Potentially useful for the treatment of urinary tract disorders, most preferably overactive bladder. Further uses include CNS, gastrointestinal or cardiovascular disorders. Another specifically claimed dihydrobenzodioxine derivative is:



287570: C₂₈ H₃₇ F N₄ O₅ S

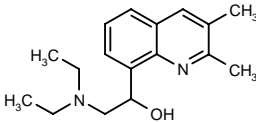
SOURCE – Roche.

REFERENCES

1. Clark, R.D. and Jahangir, A. (F. Hoffmann-La Roche AG) *Dihydrobenzodioxine carboxamide and ketone derivs. as 5-HT₄ receptor antagonists*. WO 0015636.

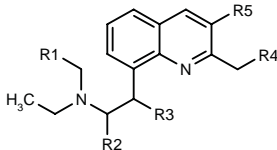
287601

2-(Diethylamino)-1-(2,3-dimethylquinolin-8-yl)ethanol



C₁₇ H₂₄ N₂ O; Mol wt: 272.3896

ACTION – Agent for the treatment of urinary incontinence with smooth muscle contractile activity; compound is reported to have a very strong contractile effect on urethral smooth muscle versus a weak effect on arterial smooth muscle, and it acts as an α -adrenoceptor ligand, with no activity on β -adrenoceptors. It is also reported to exhibit venoconstrictor activity, and is therefore potentially useful in the treatment of venous insufficiency, venous ulcer, migraine, gastrointestinal disorders and for constricting nasal mucosa. Other specifically claimed compounds from this series of 2-aminoethylquinolines include the following:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
287602	Me	H	OH	H	H		C ₁₈ H ₂₂ N ₂ O
287603	Me	H	H	H	Me		C ₁₇ H ₂₄ N ₂
287604	Me	H	OH	Me	H	(+)-1S	C ₁₇ H ₂₄ N ₂ O
287605	Me	H	OH	Me	Me	(+)-1S	C ₁₈ H ₂₆ N ₂ O
287606	H	Me	OH	H	Me	1S,2R	C ₁₇ H ₂₄ N ₂ O
287607	H	Me	OH	H	Me	1R,2R	C ₁₇ H ₂₄ N ₂ O

SOURCE – Sanofi-Synthélabo.

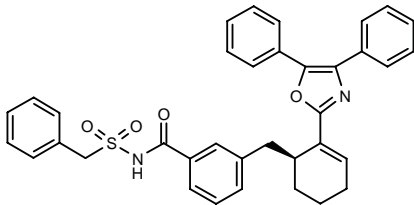
REFERENCES

1. Philippo, C. et al. (Sanofi-Synthélabo) *2-Aminoethyl-quinoline derivs., preparation and therapeutic use*. FR 2783247, WO 0015617.

TREATMENT OF RENAL DISEASES

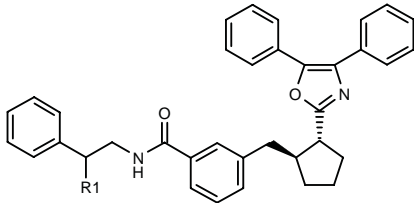
288409

N-(Benzylsulfonyl)-3-[2-(4,5-diphenyloxazol-2-yl)cyclohex-2-en-1(S)-ylmethyl]benzamide

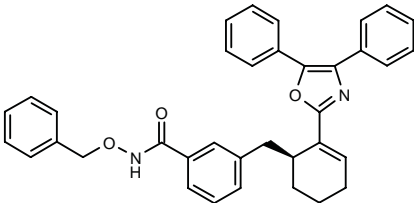


C₃₆ H₃₂ N₂ O₄ S; Mol wt: 588.7248

ACTION – Prostaglandin E₂ (PGE₂) receptor antagonist that acts especially at EP₄ receptors, giving at least 80% inhibition in a standard assay using COS-7 cells transfected with the human EP₄ receptor. Potentially useful for the treatment or prevention of mesangial proliferative glomerulonephritis, as demonstrated in rats with glomerulonephritis induced by i.v. injection of the monoclonal antibody MRC OX-7, decreasing urinary protein from 127.9 ± 12.6 mg/day in controls to 98.2 ± 20.9 mg/day and 66.4 ± 6.9 mg/day at the respective doses of 1 and 10 mg/kg administered orally every day from 5 days before to 1 day after antibody administration. Other exemplified oxazole derivatives are:



Compound	R1	Formula
288410	OH	C ₃₆ H ₃₄ N ₂ O ₃
288411	Ph	C ₄₂ H ₃₈ N ₂ O ₂



288412: C₃₆ H₃₂ N₂ O₃

SOURCE – Fujisawa.

REFERENCES

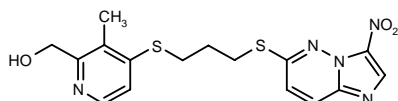
1. Hattori, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Oxazole cpds. as prostaglandin E₂ agonists or antagonists*. WO 0018744.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

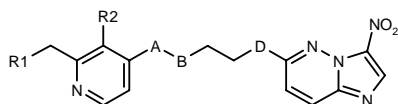
287554

[3-Methyl-4-[3-(3-nitroimidazo[1,2-*b*]pyridazin-6-ylsulfanyl)propylsulfanyl]pyridin-2-yl]methanol

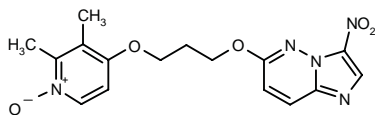


C₁₆ H₁₇ N₅ O₃ S₂; Mol wt: 391.4743

ACTION – Anti-*Helicobacter pylori* agent (MIC₅₀ = 0.05-0.5 mg/l), particularly suitable for oral administration. Complete elimination of drug was seen in 4 days following administration of 50 mg/kg/day p.o. for 3 days in mice. Other exemplified imidazopyridazines include the following:



Compound	R1	R2	A	B	D	Formula
287556	2-pyrimidinyl-S	Me	S	CH ₂	S	C ₂₀ H ₁₉ N ₇ O ₂ S ₃
287558	SCH ₂ CH ₂ OCH ₂ CH ₂ OMe	Me	S	CH ₂	S	C ₂₆ H ₃₁ N ₅ O ₈ S ₃
287562	OH	Me	O	CH ₂	S	C ₁₆ H ₁₇ N ₅ O ₄ S
287563	2-benzimidazolyl-S	Cl	CH ₂	NH	S	C ₂₂ H ₁₉ ClN ₈ O ₂ S ₂
287564	2-pyrimidinyl-S	Cl	CH ₂	NH	S	C ₁₉ H ₁₇ ClN ₈ O ₂ S ₂
287565	4-Me-2-pyrimidinyl-S	Me	S	CH ₂	S	C ₂₁ H ₂₁ N ₇ O ₂ S ₃
287566	2-benzimidazolyl-S	Cl	CH ₂	NH	O	C ₂₂ H ₂₀ Cl ₂ N ₈ O ₃ S



287561: C₁₆ H₁₇ N₅ O₅

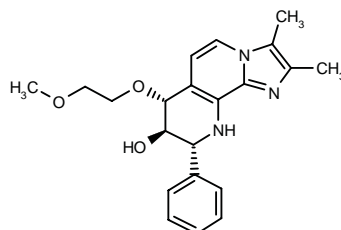
SOURCE – Byk Gulden.

REFERENCES

1. Grundler, G. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Imidazopyridazines*. US 6043242, WO 9828299.

287746

2,3-Dimethyl-7(*R*)-(2-methoxyethoxy)-9(*R*)-phenyl-7,8,9,10-tetrahydroimidazo[1,2-*h*][1,7]naphthyridin-8(*R*)-ol



C₂₁ H₂₅ N₃ O₃; Mol wt: 367.4465

ACTION – A specifically claimed tetrahydropyrido ethers with potent gastric acid secretion-inhibitory activity and excellent gastric and intestinal protective profiles. The compound exhibited 100% inhibition of pentagastrin-induced gastric acid secretion at 3 μmol/kg i.v. in perfused rat stomach *in vivo*. Potentially useful in the treatment of ulcers, gastritis and other gastrointestinal inflammatory diseases.

SOURCE – Byk Gulden.

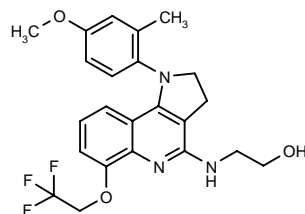
REFERENCES

1. Postius, S. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Tetrahydropyridoethers*. WO 0017200.

AU-461

288846

2-[1-(2-Methyl-4-methoxyphenyl)-6-(2,2,2-trifluoroethoxy)-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-ylamino]-1-ethanol



C₂₃ H₂₄ F₃ N₃ O₃; Mol wt: 447.4546

ACTION – Antiulcer agent, a reversible inhibitor of gastric H⁺/K⁺-ATPase (IC₅₀ = 12.15 and 4.20 μM against rabbit and pig enzyme, respectively). *In vivo*, compound was able to reduce histamine-stimulated gastric acid secretion in rats (ED₅₀ = 9.7 mg/kg i.d.) and basal gastric acid secretion in pylorus-ligated rats (ED₅₀ = 6.8 mg/kg i.d.). It demonstrated a moderate duration of action in rats upon oral administration and was seen to elevate plasma gastrin levels 4-fold over controls 6 h after dosing, remaining elevated for 10 h and returning to control levels at 12 h. In experimental models in rats, compound protected against ulcers induced by either ethanol or NaOH (ED₅₀ = 12 and 40 mg/kg p.o., respectively); by comparison, the ED₅₀ values for omeprazole under the same experimental conditions were 70 and 41 mg/kg p.o., respectively.

SOURCE – Korea Research Institute of Chemical Technology, Taejon (KR).

REFERENCES

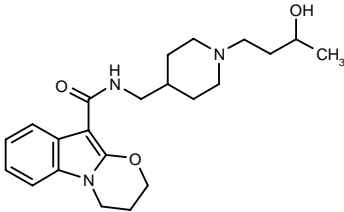
1. Choi, J.-K. et al. (Korea Research Institute of Chemical Technology) *Pyrrolo[3,2-c]-quinoline derivs. containing haloalkoxy group and pharmaceutically acceptable salts thereof*. CA 2268166, EP 0966466, JP 2000504352, US 6011044, WO 9909029.

2. Cheon, H.G. et al. *Pharmacological properties of the gastric H⁺/K⁺ ATPase inhibitor, AU-461*. Pharmacology 2000, 60(3): 161.

IRRITABLE BOWEL SYNDROME
THERAPY

287875

N-[1-(3-Hydroxybutyl)piperidin-4-ylmethyl]-3,4-dihydro-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxamide



C22 H31 N3 O3; Mol wt: 385.5049

ACTION – 5-HT₄ receptor antagonist found to have a pK_B of 9.3 for blockade of 5-HT-induced contractions of guinea pig colon longitudinal muscle-myenteric plexus preparations, while exhibiting no significant antagonism of DMPP-induced cholinergically mediated contractions. Claimed for the treatment of irritable bowel syndrome, gastroesophageal reflux disease, dyspepsia, atrial arrhythmias, stroke, anxiety and/or migraine.

SOURCE – SmithKline Beecham.

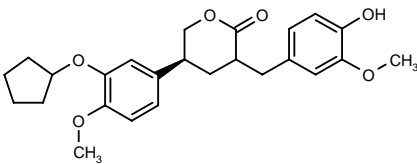
REFERENCES

1. Hossner, F. and Ryan, D.A. (SmithKline Beecham plc) *3,4-Dihydro-N-[[1-(3-hydroxybutyl)-4-piperidinyl]methyl]-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide as 5-HT₄ receptor antagonist*. WO 0017207.

INFLAMMATORY BOWEL DISEASE
THERAPY

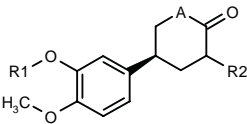
287330

5(S)-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(4-hydroxy-3-methoxybenzyl)tetrahydropyran-2-one



C25 H30 O6; Mol wt: 426.5060

ACTION – Antiinflammatory agent which modulates intracellular cAMP levels by inhibiting enzymes associated with secondary cellular messengers, i.e., cAMP phosphodiesterase, PDE4, PDE3, PDE3 and PDE4, or cGMP phosphodiesterase. It inhibited PDE4 from human U937 cells with an IC₅₀ in the range 0.1-1 μM and PDE3 from human platelets with an IC₅₀ in the range 10-100 μM. This compound inhibited human neutrophil degranulation, as demonstrated by inhibition of reactive oxygen species generation in neutrophils, with an IC₅₀ of < 1 μM, and was also shown to have a Th1-inhibiting/Th2-sustaining profile in concanavalin A-stimulated human CD4+ T-cells. *In vivo* assays demonstrated potent inhibition of resiniferitoxin-induced mouse ear edema following topical, i.p. and oral administration, with 98% inhibition at 50 μg/ear, 72% inhibition at 100 mg/kg i.p. and 45% inhibition at 10 mg/kg p.o. Furthermore, it was effective in the TNBS model of inflammatory bowel disease in rats and the mouse collagen-induced arthritis model. Other exemplified substituted γ-phenyl-δ-lactones are:



Compound	R1	R2	A	Formula
287331	cyclopentyl	H	O	C ₁₇ H ₂₂ O ₄
287332	Me	3-MeO-4-(PhCH2O)-PhCH2	NH	C ₂₈ H ₃₁ NO ₅
287333	Me	3-MeO-4-(cyclopentyl-O)-PhCH2	O	C ₂₆ H ₃₂ O ₆
287334	cyclopentyl	3,4-(OH)2-PhCH2	O	C ₂₄ H ₂₈ O ₆

SOURCE – Inflazyme.

REFERENCES

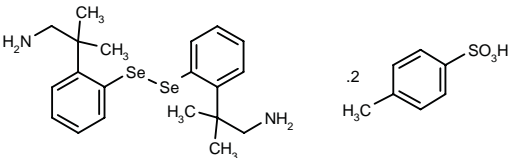
1. Shen, Y. et al. (Inflazyme Pharmaceuticals Ltd.) *Substd. gamma-phenyl-Δ-lactones and analogs thereof and uses realted thereto*. WO 0014083.

BXT-51108

287348

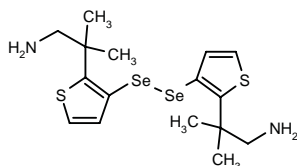
Bis[2-(2-amino-1,1-dimethylethyl)phenyl]diselenide ditosylate

2-[2-[2-[2-[2-Amino-1,1-dimetylethyl)phenyl]diselan-yl]phenyl]-2-methyl-1-propanamide ditosylate



C20 H28 N2 Se2 . 2 C7 H8 O3 S; Mol wt: 798.7816

ACTION – Antioxidant and cytoprotective agent that mimics glutathione peroxidase and antagonizes TNF-α, as demonstrated by its ability to inhibit TNF-α-induced IL-8 production and P- and E-selectin expression in human endothelial cells. Potentially useful in the treatment of inflammatory pathologies, particularly Crohn's disease and hemorrhagic rectocolitis, as well as for storing grafts for transplantation. Another specifically claimed organo-selenium compound is:



BXT-51104 [287396]: C16 H24 N2 S2 Se2

SOURCE – Oxis.

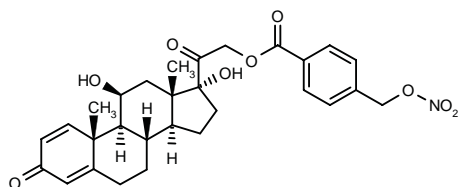
REFERENCES

1. Tailhan-Lomont, C. et al. (Oxis International, Inc.) *Aromatic diselenides and selenosulfides, their preparation and their uses, more particularly their therapeutical use.* US 6040328.

NCX-1015

287920

11 β ,17 α -Dihydroxy-21-[4-(nitrooxymethyl)benzoyloxy]-pregna-1,4-diene-3,20-dione



C29 H33 N O9; Mol wt: 539.5777

ACTION – Antiinflammatory agent, a nitric oxide (NO)-releasing derivative of prednisolone with improved antiinflammatory activity. Compound released NO in biological fluids and inhibited the formation of proinflammatory cytokines. In experimental peritonitis in mice, it was more active than prednisolone in reducing the accumulation of polymorphonuclear cells (ED_{50} = 2 and 9.5 μ g/kg i.p., respectively). In the same model, compound, but not prednisolone, reduced the CXC chemokine KC levels in the exudate (ED_{50} = 2 mg/kg i.p.) and produced a marked decrease in inducible nitric oxide synthase (iNOS) expression in inflammatory cell pellets; PGE2 and IL-1 β levels were significantly reduced by compound and prednisolone to the same extent. In addition, NCX-1015 demonstrated good relaxant activity in the guinea pig trachea precontracted with methacholine. In a model of colitis in mice induced by intracolonic injection of TNBS, compound given at doses of 0.5 and 5 mg/kg/day i.p. for 7-28 days significantly reduced disease severity as assessed by the reduction of colonic damage score, colon weight, colonic mucosal myeloperoxidase content and plasma and mucosal concentrations of IL-1 β , IL-12, IL-18, TNF- α , interferon gamma and nitrite/nitrate. Colonic iNOS expression was also significantly reduced and compound was 10-20-fold more active than prednisolone in both preventing and treating colitis.

SOURCES – NicOx; William Harvey Research Institute, London (GB).

REFERENCES

1. Burgaud, J.L. et al. *NO-steroids: A class of new anti-asthmatic agents induced bronchodilation on guinea-pig trachea in vitro.* Br J Pharmacol 2000, 129(Suppl.): Abst 28P.

2. Di Filippo, C. et al. *Effects on blood pressure and heart rate of normotensive rats by chronic treatment with prednisolone 21-[(4'-nitrooxymethyl)benzoate].* 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 68.

3. Fiorucci, S. et al. *A new nitric oxide steroid derivative (NCX-1015) with enhanced anti-inflammatory properties reduces colonic inflammation in mice.* Gastroenterology 2000, 118(4, Suppl. 2, Part 1): A587.

4. Mancini, L. et al. *Prednisolone but not NCX-1015, activates osteoclast activity in a in vitro assay.* 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 90.

5. Paul-Clarck, M.J. et al. *A nitro-derivative of prednisolone (NCX-1015) possesses higher anti-inflammatory activities.* FASEB J 2000, 14(4): Abst 491.8.

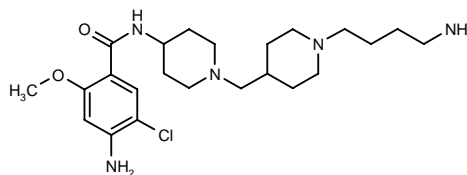
6. Paul-Clark, M.J. et al. *NCX-1015, a novel derivative of prednisolone with enhanced anti-inflammatory activity.* Br J Pharmacol 2000, 129(Suppl.): Abst 98P.

7. Perreti, M. et al. *Nitro-prednisolone is more potent than prednisolone in experimental inflammation.* 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 92.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

287729

4-Amino-N-[1-[1-(4-aminobutyl)piperidin-4-ylmethyl]piperidin-4-yl]-5-chloro-2-methoxybenzamide



C23 H38 Cl N5 O2; Mol wt: 452.0392

ACTION – 5-HT₄ receptor agonist proven to strongly accelerate lower gastrointestinal tract motility in both mice and dogs. Compound increased intestinal propulsion in mice at doses ranging from 1 to 20 mg/kg s.c.; in dogs, it increased the frequency of muscular contractions in stomach and colon at 1 mg/kg i.v. Potentially useful as a gastrointestinal prokinetic agent.

SOURCE – Dainippon Pharmaceutical.

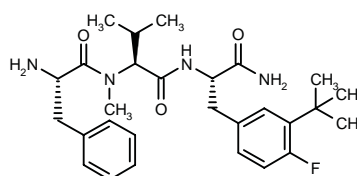
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2. Tateishi, H. et al. *Synthesis and structure-activity relationships of novel benzamide derivatives having 5-HT₄ receptor-stimulating activity.* 120th Annu Meet Pharm Soc Jpn (March 29-31, Gifu) 2000, Abst 30-PB-12-02.

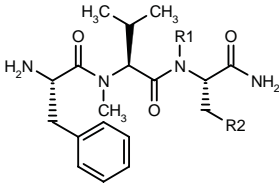
288085

L-Phenylalanyl-L-(N-methyl)valyl-L-(3-tert-butyl-4-fluoro)-phenylalaninamide



C28 H39 F N4 O3; Mol wt: 498.6391

ACTION – Potent motilin receptor antagonist, as demonstrated in a binding assay by an IC₅₀ value of 3.5 nM for inhibition of [¹²⁵I]-motilin binding in rabbit duodenal homogenates and in a functional assay by a pA₂ value of 7.58 for inhibition of acetylcholine-induced contractions of rabbit duodenal longitudinal muscle. Other specifically claimed compounds from this series of ethylamine derivatives include the following:



Compound	R1	R2	Formula
288087	H	3-i-Bu-4-OH-Ph	C ₂₈ H ₄₀ N ₄ O ₄
288089	H	3-Me-5-indolyl	C ₂₇ H ₃₆ N ₅ O ₃
288090	Me	3-Me-5-indolyl	C ₂₈ H ₃₇ N ₅ O ₃
288091	Me	4-F-3-t-Bu-Ph	C ₂₉ H ₄₁ FN ₄ O ₃
288092	Me	3-i-Bu-4-OH-Ph	C ₂₉ H ₄₂ N ₄ O ₄

SOURCE – Chugai.

REFERENCES

1. Matsuoaka, H. and Sato, T. (Chugai Pharmaceutical Co. Ltd.) *Ethylamine derivs.* WO 0017231.

SK-896

288845

H-L-Phe-L-Val-L-Pro-L-Ile-L-Phe-L-Thr-L-Tyr-Gly-L-Glu-L-Leu-L-Gln-L-Arg-L-Leu-L-Gln-L-Glu-L-Lys-L-Glu-L-Arg-L-Asn-L-Lys-Gly-L-Gln-L-Hse-OH

C125 H197 N35 O37; Mol wt: 2782.1390

ACTION – Recombinant human motilin analogue with similar affinity to motilin for rabbit gastroduodenal motilin receptors (IC₅₀ = 3.5 and 3.1 nM for compound and motilin, respectively) and a similar pharmacological profile. Compound induced contractions of smooth muscle preparations isolated from gastrointestinal tract with the following order of potency: duodenum > pylorus = jejunum = descending colon > ascending colon = ileum; it was inactive on gastric fundus and other regional organs. Its activity was species-specific: it was able to induce contractions in smooth muscle preparations isolated from rabbit duodenum but not from dogs or rats. Potentially useful as a gastroprokinetic agent.

SOURCE – Sanwa.

REFERENCES

1. Kurono, M. et al. (Sanwa Kagaku Kenkyusho Co., Ltd.) *Motilin-like polypeptide and use thereof.* EP 0378078, US 5432261.

2. Kurono, M. et al. (Sanwa Kagaku Kenkyusho Co., Ltd.) *Stabilized biologically active polypeptide and use thereof.* EP 0561130, JP 1993202095.

3. Noda, S. et al. (Sanwa Kagaku Kenkyusho Co., Ltd.) *Polypeptide derivs. having motilin-like activity and their use.* JP 1995082298.

4. Sawai, K. et al. (Sanwa Kagaku Kenkyusho Co., Ltd.) *Pharmaceutical compsns. of stabilized [Leu13]-motilin-Hse.* EP 0508435.

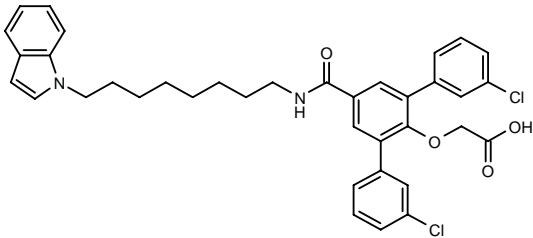
5. Tsukamoto, K. et al. *In vitro pharmacological profile of SK-896, a new human motilin analogue.* Pharmacology 2000, 60(3): 128.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

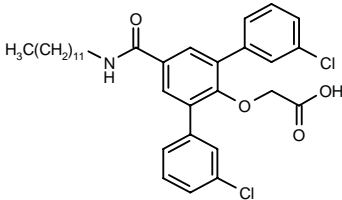
287452

[3,3’-Dichloro-5’-[8-(1*H*-indol-1-yl)octylcarbamoyl]-[1,1’:3’,1’’-terphenyl]-2’-yloxy]acetic acid



C37 H36 Cl2 N2 O4; Mol wt: 643.6074

ACTION – Potent protein-tyrosine-phosphatase PTP1B inhibitor (IC₅₀ = 137 nM) with promising *in vivo* activity. Potentially useful for the treatment of insulin resistance associated with obesity, glucose intolerance and type 2 diabetes. Another terphenyl PTP1B inhibitor is:



287450: C33 H39 Cl2 N O4

SOURCE – Wyeth-Ayerst.

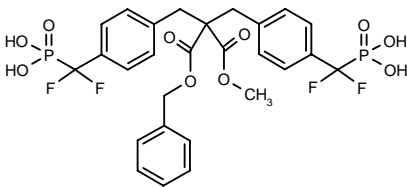
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1. Butera, J.A. et al. (American Home Products Corp.) *2,3,5-Substd. biphenyls useful in the treatment of insulin resistance and hyperglycemia.* WO 9961410.

2. Gundersen, G. et al. *Design and synthesis of novel terphenyl PTPase 1B inhibitors for the treatment of type II diabetes-III: Tailpiece modifications.* 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 249.

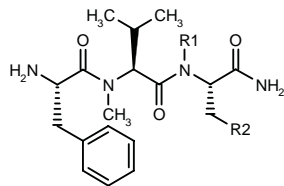
287844

2,2-Bis[1,1-difluoro-1-(phosphono)methyl]benzyl]malonic acid benzyl methyl diester



C27 H26 F4 O10 P2; Mol wt: 648.4324

ACTION – Potent motilin receptor antagonist, as demonstrated in a binding assay by an IC₅₀ value of 3.5 nM for inhibition of [¹²⁵I]-motilin binding in rabbit duodenal homogenates and in a functional assay by a pA₂ value of 7.58 for inhibition of acetylcholine-induced contractions of rabbit duodenal longitudinal muscle. Other specifically claimed compounds from this series of ethylamine derivatives include the following:



Compound	R1	R2	Formula
288087	H	3-i-Bu-4-OH-Ph	C ₂₈ H ₄₀ N ₄ O ₄
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288090	Me	3-Me-5-indolyl	C ₂₈ H ₃₇ N ₅ O ₃
288091	Me	4-F-3-t-Bu-Ph	C ₂₉ H ₄₁ FN ₄ O ₃
288092	Me	3-i-Bu-4-OH-Ph	C ₂₉ H ₄₂ N ₄ O ₄

SOURCE – Chugai.

REFERENCES

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SK-896

288845

H-L-Phe-L-Val-L-Pro-L-Ile-L-Phe-L-Thr-L-Tyr-Gly-L-Glu-L-Leu-L-Gln-L-Arg-L-Leu-L-Gln-L-Glu-L-Lys-L-Glu-L-Arg-L-Asn-L-Lys-Gly-L-Gln-L-Hse-OH

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SOURCE – Sanwa.

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4. Sawai, K. et al. (Sanwa Kagaku Kenkyusho Co., Ltd.) *Pharmaceutical compsns. of stabilized [Leu13]-motilin-Hse.* EP 0508435.

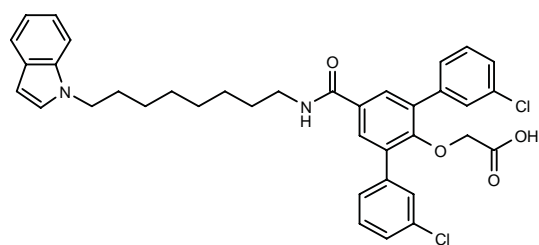
5. Tsukamoto, K. et al. *In vitro pharmacological profile of SK-896, a new human motilin analogue.* Pharmacology 2000, 60(3): 128.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

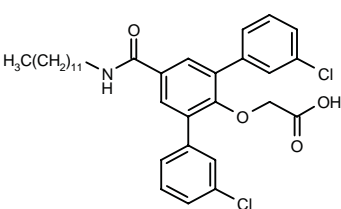
287452

[3,3''-Dichloro-5'-[8-(1*H*-indol-1-yl)octylcarbamoyl]-[1,1':3',1''-terphenyl]-2'-yloxy]acetic acid



C37 H36 Cl2 N2 O4; Mol wt: 643.6074

ACTION – Potent protein-tyrosine-phosphatase PTP1B inhibitor (IC₅₀ = 137 nM) with promising *in vivo* activity. Potentially useful for the treatment of insulin resistance associated with obesity, glucose intolerance and type 2 diabetes. Another terphenyl PTP1B inhibitor is:



287450: C33 H39 Cl2 N O4

SOURCE – Wyeth-Ayerst.

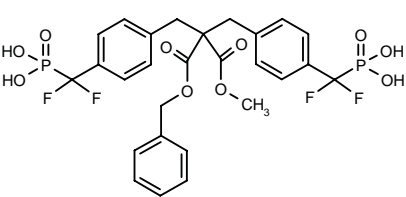
REFERENCES

1. Butera, J.A. et al. (American Home Products Corp.) *2,3,5-Substd. biphenyls useful in the treatment of insulin resistance and hyperglycemia.* WO 9961410.

2. Gundersen, G. et al. *Design and synthesis of novel terphenyl PTPase 1B inhibitors for the treatment of type II diabetes-III: Tailpiece modifications.* 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 249.

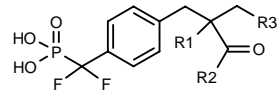
287844

2,2-Bis[1,1-difluoro-1-(phosphono)methyl]benzyl]malonic acid benzyl methyl diester



C27 H26 F4 O10 P2; Mol wt: 648.4324

ACTION – Protein-tyrosine-phosphatase PTP1B inhibitor that improves insulin sensitivity and is thus expected to be useful for the prevention of type 1 and type 2 diabetes mellitus and as an antiobesity agent. Other exemplified phosphonic acid derivatives include the following:



Compound	R1	R2	R3	Formula
287846	CONHCH2Ph	OMe	4-[(HO)2POCF2]-Ph	C ₂₇ H ₂₇ F ₄ NO ₉ P ₂
287848	CO2CH2Ph	OCH2Ph	Ph	C ₃₂ H ₂₉ F ₂ O ₇ P
287849	CO2CH2Ph	OCH2Ph	4-(EtSO2CH2)-Ph	C ₃₅ H ₃₅ F ₂ O ₉ PS
287850	CO2CH2Ph	OCH2Ph	4-CF3-Ph	C ₃₃ H ₂₈ F ₅ O ₇ P
287852	CO2CH2Ph	OCH2Ph	1,3-dioxo-2-isoindolinyl	C ₃₄ H ₂₈ F ₂ NO ₉ P
287853	Ph	Ph	4-[(HO)2POCF2]-Ph	C ₃₀ H ₂₆ F ₄ O ₇ P ₂
287854	Ph	Ph	4-(NH2SO2)-Ph	C ₂₉ H ₂₆ F ₂ NO ₆ PS
287855	Ph	Ph	4-CO2H-Ph	C ₃₀ H ₂₅ F ₂ O ₆ P
287856	4-F-Ph	4-F-Ph	4-[(HO)2POCF2]-Ph	C ₃₁ H ₂₆ F ₆ O ₇ P ₂

SOURCE – Merck Frosst.

REFERENCES

1. Leblanc, Y. et al. (Merck Frosst Canada Inc.) *Phosphonic acids derivs. as inhibitors of PTP-1B*. WO 0017211.

288055

L-Histidyl-L-alanyl-L-glutamyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-glutamyl-glycyl-L-glutaminy-L-alanyl-L-alanyl-N^ε-(N^α-hexadecanoyl-γ-L-glutamyl)-L-lysyl-L-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginyl-glycyl-L-arginyl-glycine

C172 H265 N43 O51; Mol wt: 3751.2360

ACTION – Glucagon-like peptide-1 (GLP-1) derivative with picomolar potency against the cloned human GLP-1 receptor expressed in BHK cells (IC₅₀ = 61 pM). Compound exhibited a longer plasma half-life compared to the parent compound and appears to be a suitable once-daily agent for the treatment of type 2 diabetes. Other GLP-1 derivatives include the following:

L-Histidyl-L-alanyl-L-glutamyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-glutamyl-glycyl-L-glutaminy-L-alanyl-L-alanyl-L-arginyl-L-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-N^ε-(N^α-hexadecanoyl-γ-L-glutamyl)-L-lysyl-glycyl-L-arginyl-glycine

288056: C172 H265 N43 O51

L-Histidyl-L-alanyl-L-glutamyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-glutamyl-glycyl-L-glutaminy-L-alanyl-L-alanyl-L-arginyl-L-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginyl-glycyl-N^ε-(N^α-hexadecanoyl-γ-L-glutamyl)-L-lysine

288058: C170 H262 N42 O50

SOURCE – Novo Nordisk.

REFERENCES

1. Knudsen, L.B. et al. (Novo Nordisk A/S) *GLP-1 derivs. with helix-content exceeding 25%, forming partially structured micellar-like aggregates*. WO 9943341, WO 9943706.

2. Knudsen, L.B. et al. *Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration*. J Med Chem 2000, 43(9): 1664.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

TT-01024

287393

N-[3(E)-Hexenoyl]-L-Tyr-L-Ala-L-Asp-L-Ala-L-Ile-L-Phe-L-Thr-L-Asn-L-Ser-L-Tyr-L-Arg-L-Lys-L-Val-L-Leu-Gly-L-Gln-L-Leu-L-Ser-L-Ala-L-Arg-L-Lys-L-Leu-L-Leu-L-Gln-L-Asp-L-Ile-L-Met-L-Ser-L-Arg-NH₂

(Hexenoyl *trans*-3)-hGRF(1-29)NH₂

C155 H254 N44 O43 S; Mol wt: 3454.0420

ACTION – Chimeric fatty body-growth hormone-releasing factor (GRF) analogue that is biodegradable and non-immunogenic and exhibits increased biological potency, for use as an anabolic agent and in the diagnosis and treatment of GH deficiency. Results from testing in several assays in pigs demonstrated that compound acts as a potent GH secretagogue, with a longer duration of action than hGRF(1-29)NH₂.

SOURCE – Theratechnologies.

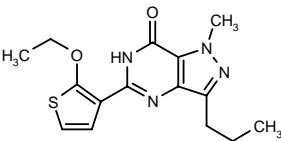
REFERENCES

1. Gravel, D. et al. (Theratechnologies Inc.) *GRF analogs with increased biological potency*. WO 0014236.

TREATMENT OF MALE SEXUAL DYSFUNCTION

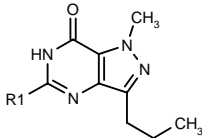
287216

5-(2-Ethoxythien-3-yl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



C15 H18 N4 O2 S; Mol wt: 318.3992

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC_{50} = 0.47 μ M against rabbit enzyme) claimed for the treatment of sexual dysfunction, particularly male erectile dysfunction, as well as heart failure, pulmonary hypertension and angina. Other compounds from this series of 5-heterocyclyl pyrazolo[4,3-d]pyrimidin-7-ones include the following:



Compound	R1	Formula
287217	7-EtO-2-benzofuryl	C ₁₉ H ₂₀ N ₄ O ₃
287218	3-EtO-5-[4-(NH2CO)-1-Pip-SO2]-2-thienyl	C ₂₁ H ₂₈ N ₆ O ₅ S ₂

SOURCE – Ortho-McNeil.

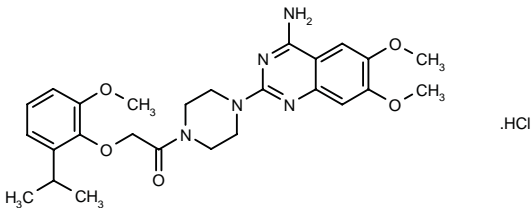
REFERENCES

1. Sui, Z. et al. (Ortho-McNeil Pharmaceutical, Inc.) *5-Heterocyclyl pyrazolo[4,3-d]pyrimidin-7-ones for the treatment of male erectile dysfunction*. US 6077841, WO 0014088.

REC-15/2615^{3,5,6,8}

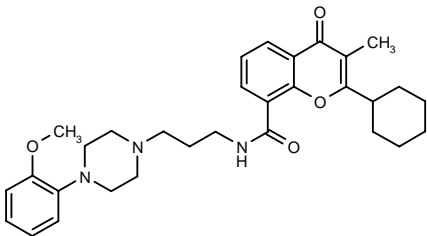
287385

1-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]-2-[2-(isopropyl)-6-methoxyphenoxy]ethan-1-one hydrochloride

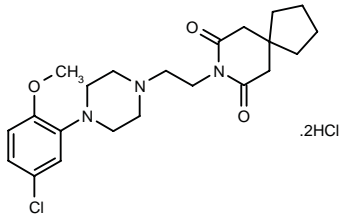


C26 H33 N5 O5 . HCl; Mol wt: 532.0376

ACTION – α_1 -Adrenoceptor antagonist with selective affinity for the α_{1B} subtype over α_{1A} , α_{1D} and α_{1L} subtypes (pK_i = 9.35, 8.12, 7.99 and 7.31, respectively). *In vivo*, compound increased intracavernous pressure in both rats and dogs at doses devoid of effects on blood pressure. The approximate ED_{25} values (doses inducing 25% increase in the ratio intracavernous pressure/blood pressure) were 22 μ g/kg for compound, 136 μ g/kg for prazosin and 1298 μ g/kg for phentolamine. Potentially useful for the treatment of erectile dysfunction. Other related compounds are:



Rec-15/2841 [287388]^{1,2,4,6,8,9}; C31 H39 N3 O4



Rec-15/3039 [287389]^{7,8}: C22 H30 Cl N3 O3 . 2HCl

SOURCE – Recordati.

REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) *Bicyclic heterocyclic derivs. having α_1 -adrenergic and 5HT_{1A}*. US 5474994.

2. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) *Heterobicyclic cpds. as antagonists of α_1 -adrenergic and 5HT_{1A} receptors*. EP 0558245, JP 1994009606, US 5403842, US 5605896, WO 9317007.

3. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) *Quinazolinyl-amino derivs. having α -antagonist activity*. EP 0750614, JP 1997511238, US 5798362, WO 9525726.

4. Hieble, J.P. et al. *Effects of α_1 adrenoceptor antagonists on agonist and tilt-induced changes in blood pressure: Relationships to uroselectivity*. Eur J Pharmacol 1999, 373(1): 51.

5. Leonardi, A. et al. *Synthesis, pharmacological evaluation, and structure-activity relationship and quantitative structure-activity relationship studies on novel derivatives of 2,4-diamino-6,7-dimethoxyquinazoline α_1 -adrenoceptor antagonists*. J Med Chem 2000, 42(3): 427.

6. Menziani, M.C. et al. *Relevance of theoretical molecular descriptors in quantitative structure-activity relationship analysis of α_1 -adrenergic receptor antagonists*. Bioorg Med Chem 1999, 7(11): 2437.

7. Rossier, O. et al. *Inverse agonism and neutral antagonism at α_{1A} and α_{1B} -adrenergic receptors*. Mol Pharmacol 1999, 56(5): 858.

8. Sironi, G. et al. *Effects of intracavernous administration of selective antagonists of α_1 -adrenoceptor subtypes on erection in anesthetized rats and dogs*. J Pharmacol Exp Ther 2000, 292(3): 974.

9. Testa, R. et al. *Antagonism to noradrenaline-induced lethality in rats is related to affinity for the α_{1A} -adrenoceptor subtype*. Life Sci 1997, 61(22): 2177.

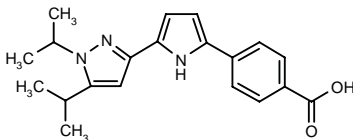
DERMATOLOGIC DRUGS

ANTIPSORIATICS

ER-38930*

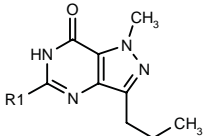
248732

4-[5-(1,5-Diisopropylpyrazol-3-yl)-1 H-pyrrol-2-yl]benzoic acid



C20 H23 N3 O2; Mol wt: 337.4250

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC_{50} = 0.47 μ M against rabbit enzyme) claimed for the treatment of sexual dysfunction, particularly male erectile dysfunction, as well as heart failure, pulmonary hypertension and angina. Other compounds from this series of 5-heterocyclyl pyrazolo[4,3-d]pyrimidin-7-ones include the following:



Compound	R1	Formula
287217	7-EtO-2-benzofuryl	C ₁₉ H ₂₀ N ₄ O ₃
287218	3-EtO-5-[4-(NH ₂ CO)-1-Pip-SO ₂]-2-thienyl	C ₂₁ H ₂₈ N ₆ O ₅ S ₂

SOURCE – Ortho-McNeil.

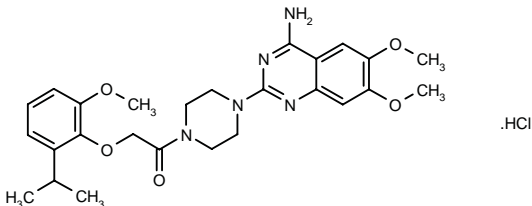
REFERENCES

1. Sui, Z. et al. (Ortho-McNeil Pharmaceutical, Inc.) 5-Heterocyclyl pyrazolo[4,3-d]pyrimidin-7-ones for the treatment of male erectile dysfunction. US 6077841, WO 0014088.

REC-15/2615^{3,5,6,8}

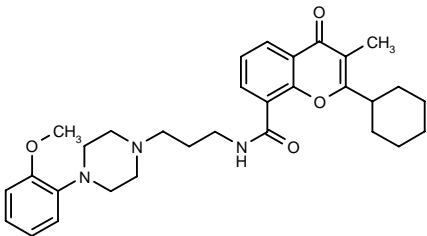
287385

1-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]-2-[2-(isopropyl)-6-methoxyphenoxy]ethan-1-one hydrochloride

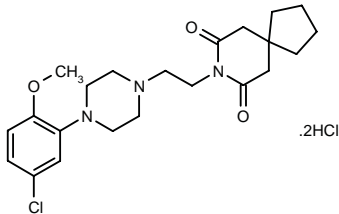


C26 H33 N5 O5 . HCl; Mol wt: 532.0376

ACTION – α_1 -Adrenoceptor antagonist with selective affinity for the α_{1B} subtype over α_{1A} , α_{1D} and α_{1L} subtypes (pK_i = 9.35, 8.12, 7.99 and 7.31, respectively). *In vivo*, compound increased intracavernous pressure in both rats and dogs at doses devoid of effects on blood pressure. The approximate ED_{25} values (doses inducing 25% increase in the ratio intracavernous pressure/blood pressure) were 22 μ g/kg for compound, 136 μ g/kg for prazosin and 1298 μ g/kg for phentolamine. Potentially useful for the treatment of erectile dysfunction. Other related compounds are:



Rec-15/2841 [287388]^{1,2,4,6,8,9}: C31 H39 N3 O4



Rec-15/3039 [287389]^{7,8}: C22 H30 Cl N3 O3 . 2HCl

SOURCE – Recordati.

REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) Bicyclic heterocyclic derivs. having α_1 -adrenergic and $5HT_{1A}$. US 5474994.

2. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) Heterobicyclic cpds. as antagonists of α_1 -adrenergic and $5HT_{1A}$ receptors. EP 0558245, JP 1994009606, US 5403842, US 5605896, WO 9317007.

3. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) Quinazolinyl-amino derivs. having α -antagonist activity. EP 0750614, JP 1997511238, US 5798362, WO 9525726.

4. Hieble, J.P. et al. Effects of α_1 adrenoceptor antagonists on agonist and tilt-induced changes in blood pressure: Relationships to uroselectivity. Eur J Pharmacol 1999, 373(1): 51.

5. Leonardi, A. et al. Synthesis, pharmacological evaluation, and structure-activity relationship and quantitative structure-activity relationship studies on novel derivatives of 2,4-diamino-6,7-dimethoxyquinazoline α_1 -adrenoceptor antagonists. J Med Chem 2000, 42(3): 427.

6. Menziani, M.C. et al. Relevance of theoretical molecular descriptors in quantitative structure-activity relationship analysis of α_1 -adrenergic receptor antagonists. Bioorg Med Chem 1999, 7(11): 2437.

7. Rossier, O. et al. Inverse agonism and neutral antagonism at α_{1A} and α_{1B} -adrenergic receptors. Mol Pharmacol 1999, 56(5): 858.

8. Sironi, G. et al. Effects of intracavernous administration of selective antagonists of α_1 -adrenoceptor subtypes on erection in anesthetized rats and dogs. J Pharmacol Exp Ther 2000, 292(3): 974.

9. Testa, R. et al. Antagonism to noradrenaline-induced lethality in rats is related to affinity for the α_{1A} -adrenoceptor subtype. Life Sci 1997, 61(22): 2177.

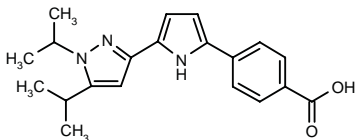
DERMATOLOGIC DRUGS

ANTIPSORIATICS

ER-38930*

248732

4-[5-(1,5-Diisopropylpyrazol-3-yl)-1H-pyrrol-2-yl]benzoic acid



C20 H23 N3 O2; Mol wt: 337.4250

ACTION – Retinoic acid receptor RAR α agonist with affinity for RAR α receptors 13-fold lower than that of *all-trans*-retinoic acid (ATRA; IC₅₀ relative to ATRA = 13) and good selectivity over RAR β and RAR γ receptor subtypes. In a transactivation assay, compound showed higher activity than ATRA at RAR α (EC₅₀ relative to ATRA = 0.19) with high selectivity relative to RAR β and RAR γ . It exhibited highly potent cell differentiation-inducing activity in HL-60 cells (EC₅₀ = 0.27 nM). Potentially useful as a lead compound for the development of RAR α -selective retinoids for use in the treatment of dermatological diseases such as psoriasis, cancer and immunological disorders.

SOURCE – Eisai.

REFERENCES

1. Kikuchi, K. et al. (Eisai Co., Ltd.) *Heterocyclic carboxylic acid derivs. and drugs containing the same*. JP 1997071566, US 5977108, WO 9702244.

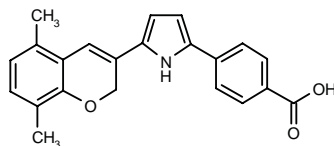
2. Kikuchi, K. et al. *Novel retinoic acid receptor α agonists: Syntheses and evaluation of pyrazole derivatives*. Bioorg Med Chem Lett 2000, 10(7): 619.

*Identified compound **248732** (see **247716**) Drug Data Rep 1997, 019(06): 0562.

ER-41666

288479

4-[5-(5,8-Dimethyl-2*H*-1-benzopyran-3-yl)-1*H*-pyrrol-2-yl]-benzoic acid



C22 H19 N O3; Mol wt: 345.3961

ACTION – Potent and selective retinoic acid receptor RAR α agonist with binding affinity about 10-fold higher than *all-trans*-retinoic acid (ATRA) and approximately 2-fold higher potency than ATRA in functional tests. Considered a lead for the development of clinically useful agents for the treatment of dermatological diseases and immunological disorders.

SOURCE – Eisai.

REFERENCES

1. Tagami, K. et al. (Eisai Co., Ltd.) *Fused-ring carboxylic acid derivs*. EP 0889032, WO 9734869.

2. Yamauchi, T. et al. (Eisai Co., Ltd.) *Methods for preventing, inhibiting or treating graft rejection reactions in graft-versus-host disease (GVHD) and organ transplantation*. EP 0930075, JP 1998158192, WO 9814214.

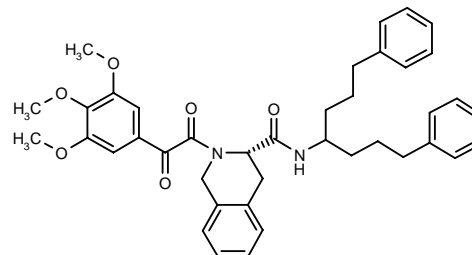
3. Yamauchi, T. et al. (Eisai Co., Ltd.) *Retinoic acid agonists as preventive and therapeutic agents for nephritis*. JP 2000154150, WO 9920309.

4. Hibi, S. et al. *Syntheses and evaluation of naphthalenyl- and chromenyl-pyrrolyl-benzoic acids as potent and selective retinoic acid receptor alpha agonists*. Bioorg Med Chem Lett 2000, 10(7): 623.

HAIR GROWTH STIMULANTS

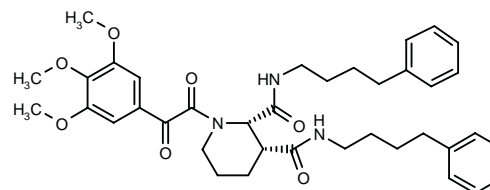
288259

2-[2-Oxo-2-(3,4,5-trimethoxyphenyl)acetyl]-*N*-[4-phenyl-1-(3-phenylpropyl)butyl]-1,2,3,4-tetrahydroisoquinoline-3(*S*)-carboxamide

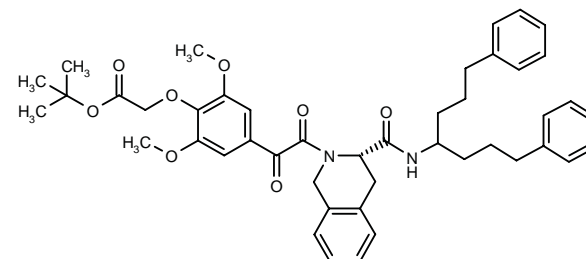


C40 H44 N2 O6; Mol wt: 648.7956

ACTION – Agent for the treatment of hair loss, found to arrest and/or reverse hair loss or promote hair growth without immunosuppressive activity. It is also claimed to be useful for the treatment or prevention of multidrug resistance. Other exemplified 2-substituted heterocyclic ketoamides include the following:



288260: C38 H47 N3 O7



288261: C45 H52 N2 O8

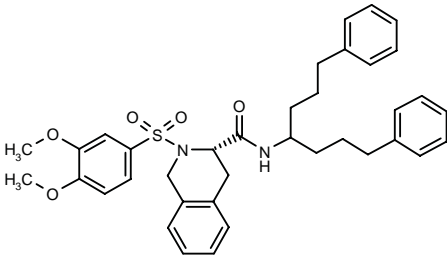
SOURCE – Procter & Gamble.

REFERENCES

1. McIver, J.M. et al. (The Procter & Gamble Co.) *Heterocyclic 2-substd. ketoamides useful for treating hair loss in mammals*. WO 0018733.

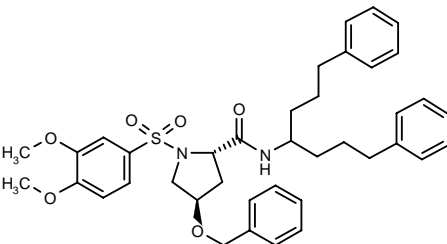
288262

2-(3,4-Dimethoxyphenylsulfonyl)-N-[4-phenyl-1-(3-phenylpropyl)butyl]-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide

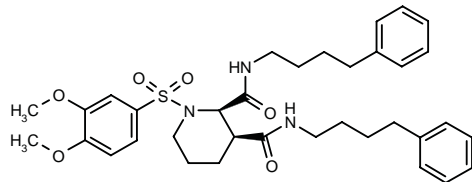


C37 H42 N2 O5 S; Mol wt: 626.8138

ACTION – Agent for the treatment of hair loss found to arrest and/or reverse hair loss or promote hair growth without exerting immunosuppressive activity. It is also claimed to be useful for the treatment or prevention of multidrug resistance. Other exemplified 2-substituted heterocyclic sulfonamides include the following:



288263: C39 H46 N2 O6 S



288264: C35 H45 N3 O6 S

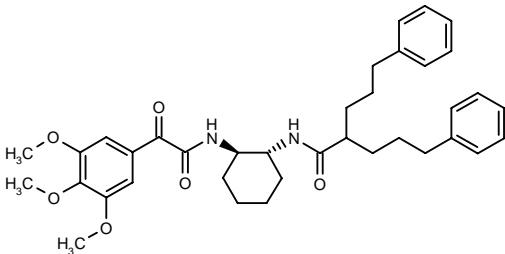
SOURCE – Procter & Gamble.

REFERENCES

1. McIver, J.M. et al. (The Procter & Gamble Co.) *2-Substd. heterocyclic sulfonamides*. WO 0018735.

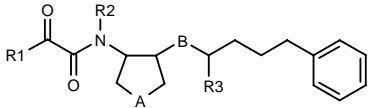
288365

trans-N-[2-[2-Oxo-2-(3,4,5-trimethoxyphenyl)aceta-mido]cyclohexyl]-5-phenyl-2-(3-phenylpropyl)pentan-amide



C37 H46 N2 O6; Mol wt: 614.7784

ACTION – Agent for the treatment of hair loss, found to arrest and/or reverse hair loss or promote hair growth without immunosuppressive activity. It is also claimed to be useful for the treatment or prevention of multidrug resistance. Other exemplified 2-substituted ketoamides include the following:



Compound	R1	R2	R3	A	B	Isomer	Formula
288367	3,4,5-(MeO)3-Ph	H	H	-CH2-	-CONH-	cis	C ₂₇ H ₃₄ N ₂ O ₆
288368	3,4,5-(MeO)3-Ph	H	(CH2)3-Ph	-(CH2)2-	-CONH-	cis	C ₃₇ H ₄₈ N ₂ O ₆
288369	3,4,5-(MeO)3-Ph	H	CO2-CH2Ph	-CH2-	-CONH-	cis	C ₃₅ H ₄₀ N ₂ O ₈
288370	Ph	Me	H	-(CH2)2-	-N(Me)-CO-	trans	C ₂₇ H ₃₄ N ₂ O ₃
288371	2-furyl	Me	H	-(CH2)2-	-N(Me)-CO-	trans	C ₂₅ H ₃₂ N ₂ O ₄

SOURCE – Procter & Gamble.

REFERENCES

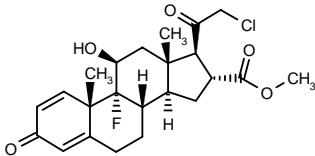
1. Degenhardt, C.R. et al. (The Procter & Gamble Co.) *2-Substd. ketoamides*. WO 0018725.

TOPICAL ANTINFLAMMATORY AGENTS

FDPCICM

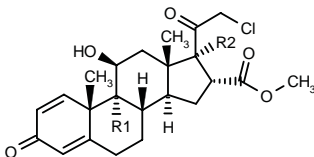
288013

21-Chloro-9α-fluoro-11β-hydroxy-3,20-dioxo-1,4-pregna-diene-16α-carboxylic acid methyl ester



C23 H28 Cl F O5; Mol wt: 438.9202

ACTION – Topical steroidal antiinflammatory antedrug, a prednisolone derivative incorporating a metabolically labile group into the corticosteroid nucleus to provide a locally active compound that is hydrolyzed to inactive acid metabolites upon entry into the systemic circulation. Compound retained the antiinflammatory activity of prednisolone following single topical application in the croton oil-induced mouse ear edema model, with an ID₅₀ value of 346 nmol versus 540 nmol for prednisolone. Furthermore, in contrast to the parent compound, the antedrug showed no significant systemic side effects, i.e., effects on body weight gain, thymus weight and plasma corticosterone levels, in the 5-day croton oil ear edema assay. Other modified 21-desoxy-21-chloro-prednisolone derivatives include the following:



Compound	R1	R2	Formula
PCICM [288017]	H	OH	C ₂₃ H ₂₈ ClO ₆
FPCICM [288018]	F	OH	C ₂₃ H ₂₈ ClFO ₆
DPCICM [288019]	H	H	C ₂₃ H ₂₈ ClO ₅

SOURCE – Florida A&M University, Tallahassee, FL (US).

REFERENCES

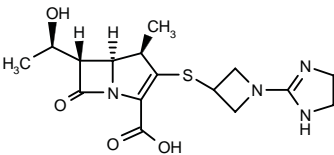
1. Ko, D.H. et al. *New steroidal anti-inflammatory antedugs: Methyl 21-desoxy-21-chloro-11β,17α-dihydroxy-3,20-dioxo-1,4-pregnadiene-16α-carboxylate, methyl 21-desoxy-21-chloro-11β-hydroxy-3,20-dioxo-1,4-pregnadiene-16α-carboxylate, and their 9α-fluoro derivatives*. Steroids 2000, 65(4): 210.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

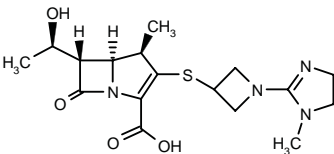
287625

(1*R*,5*S*,6*S*)-2-[1-(4,5-Dihydro-1*H*-imidazol-2-yl)azetidin-3-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid



C16 H22 N4 O4 S; Mol wt: 366.4398

ACTION – Carbapenem antibiotic exhibiting potent antibacterial activity against Gram-positive and Gram-negative microorganisms, as well as excellent resistance to β-lactamases and renal dehydropeptidase (DHP) and low toxicity. Compound displayed MIC values of 0.025 µg/ml, 0.006 µg/ml or less, 0.025 µg/ml, 0.025 µg/ml, 0.05 µg/ml, 0.025 µg/ml and 1.56 µg/ml, respectively, against *Staphylococcus aureus* FDA 209 JC-1, *Streptococcus pyogenes* Cook, *Bacillus subtilis* ATCC 6633, *Escherichia coli* NIHJ JC-2, *Klebsiella pneumoniae* PC1-602, *Salmonella typhi* 901 and *Pseudomonas aeruginosa* IFO 3445. Another exemplified compound is:



287626: C17 H24 N4 O4 S

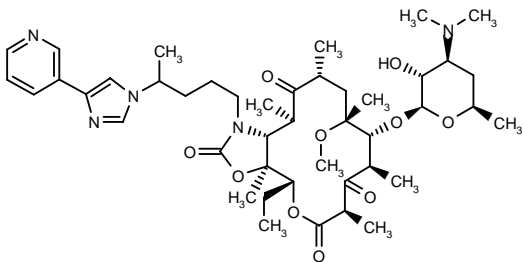
SOURCE – Wyeth-Lederle Japan.

REFERENCES

1. Abe, T. et al. (Wyeth-Lederle Japan, Ltd.) *Carbapenem cpds*. WO 0015640.

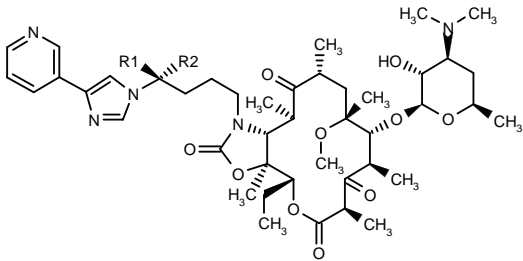
287889

3-Des(hexopyranosyloxy)-11-deoxo-6-*O*-methyl-3-oxo-11-[4-[4-(pyridin-3-yl)imidazol-1-yl]pentylamino]erythro-mycin A 11-*N*,12-*O*-cyclic carbamate



C44 H67 N5 O10; Mol wt: 826.0383

ACTION – Macrolide antibiotic claimed for the treatment of bacterial and protozoal infections, as well as cancer and atherosclerosis. Other exemplified compounds from this series of carbamate and carbazate ketolides include the following:

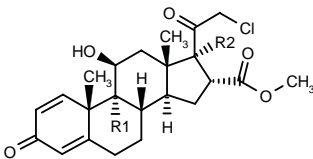


Compound	R1	R2	Formula
287890	H	Me	C ₄₄ H ₆₇ N ₅ O ₁₀
287891	Me	H	C ₄₄ H ₆₇ N ₅ O ₁₀

SOURCE – Pfizer.

REFERENCES

1. Kaneko, T. et al. (Pfizer Products Inc.) *Carbamate and carbazate ketolide antibiotics*. WO 0017218.



Compound	R1	R2	Formula
PCICM [288017]	H	OH	C ₂₃ H ₂₉ ClO ₆
FPCICM [288018]	F	OH	C ₂₃ H ₂₈ ClFO ₆
DPCICM [288019]	H	H	C ₂₃ H ₂₉ ClO ₅

SOURCE – Florida A&M University, Tallahassee, FL (US).

REFERENCES

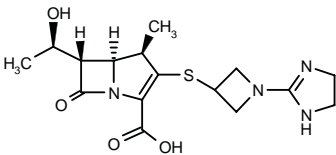
1. Ko, D.H. et al. *New steroidal anti-inflammatory antedugs: Methyl 21-desoxy-21-chloro-11β,17α-dihydroxy-3,20-dioxo-1,4-pregnadiene-16α-carboxylate, methyl 21-desoxy-21-chloro-11β-hydroxy-3,20-dioxo-1,4-pregnadiene-16α-carboxylate, and their 9α-fluoro derivatives.* Steroids 2000, 65(4): 210.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

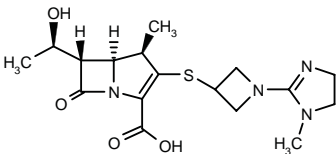
287625

(1*R*,5*S*,6*S*)-2-[1-(4,5-Dihydro-1*H*-imidazol-2-yl)azetidin-3-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid



C16 H22 N4 O4 S; Mol wt: 366.4398

ACTION – Carbapenem antibiotic exhibiting potent antibacterial activity against Gram-positive and Gram-negative microorganisms, as well as excellent resistance to β-lactamases and renal dehydropeptidase (DHP) and low toxicity. Compound displayed MIC values of 0.025 μg/ml, 0.006 μg/ml or less, 0.025 μg/ml, 0.025 μg/ml, 0.05 μg/ml, 0.025 μg/ml and 1.56 μg/ml, respectively, against *Staphylococcus aureus* FDA 209 JC-1, *Streptococcus pyogenes* Cook, *Bacillus subtilis* ATCC 6633, *Escherichia coli* NIHJ JC-2, *Klebsiella pneumoniae* PC1-602, *Salmonella typhi* 901 and *Pseudomonas aeruginosa* IFO 3445. Another exemplified compound is:



287626: C17 H24 N4 O4 S

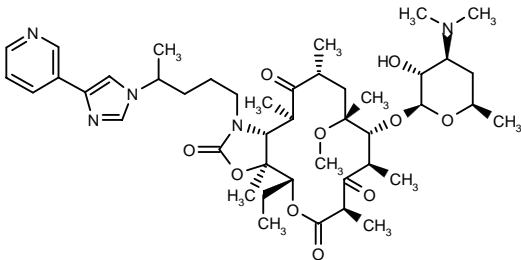
SOURCE – Wyeth-Lederle Japan.

REFERENCES

1. Abe, T. et al. (Wyeth-Lederle Japan, Ltd.) *Carbapenem cpds.* WO 0015640.

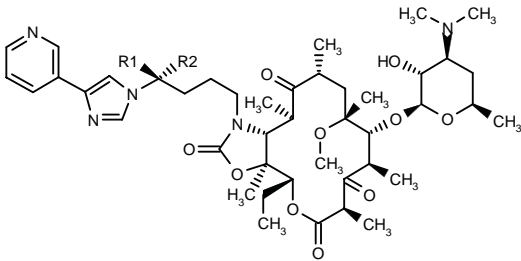
287889

3-Des(hexopyranosyloxy)-11-deoxo-6-*O*-methyl-3-oxo-11-[4-[4-(pyridin-3-yl)imidazol-1-yl]pentylamino]erythromycin A 11-*N*,12-*O*-cyclic carbamate



C44 H67 N5 O10; Mol wt: 826.0383

ACTION – Macrolide antibiotic claimed for the treatment of bacterial and protozoal infections, as well as cancer and atherosclerosis. Other exemplified compounds from this series of carbamate and carbazate ketolides include the following:



Compound	R1	R2	Formula
287890	H	Me	C ₄₄ H ₆₇ N ₅ O ₁₀
287891	Me	H	C ₄₄ H ₆₇ N ₅ O ₁₀

SOURCE – Pfizer.

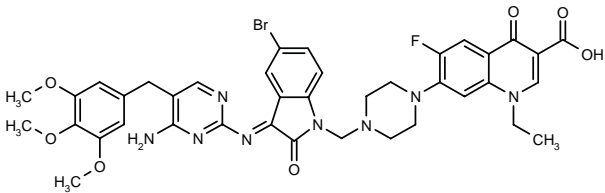
REFERENCES

1. Kaneko, T. et al. (Pfizer Products Inc.) *Carbamate and carbazate ketolide antibiotics.* WO 0017218.

ANTIBACTERIAL DRUGS

287256

7-[4-[3-[4-Amino-5-(3,4,5-trimethoxybenzyl)pyrimidin-2-ylimino]-5-bromo-2-oxo-2,3-dihydro-1*H*-indol-1-ylmethyl]-piperazin-1-yl]-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C39 H38 Br F N8 O7; Mol wt: 829.6802

M.p. 141 °C.

ACTION – Antibacterial agent, a Mannich base of norfloxacin with broad-spectrum antibacterial activity against Gram-positive and Gram-negative organisms including *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Escherichia coli*, *Salmonella paratyphi* A and *Bacillus subtilis*, against which it exhibited superior activity compared to norfloxacin. Compound was more active than norfloxacin in protecting against systemic infections induced by *E. coli* in mice (ED₅₀ = 1.62 and 6.0 mg/kg p.o., respectively). In addition, it exhibited significant antifungal activity superior to the reference compound clotrimazole against *Histoplasma capsulatum* (MIC = 2.44 and 19.53 µg/ml, respectively), as well as good anti HIV activity (IC₅₀ = 13.9 µg/ml in MT-4 cells).

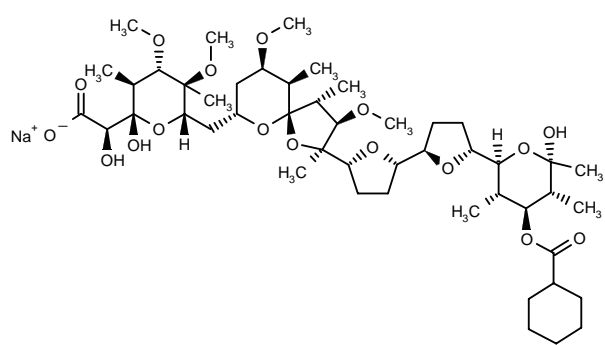
SOURCES – Banaras Hindu University, Varanasi (IN); Katholieke Universiteit Leuven, Leuven (BE).

REFERENCES

1. Pandeya, S.N. et al. *Synthesis, antibacterial, antifungal and anti-HIV activities for norfloxacin Mannich bases*. Eur J Med Chem 2000, 35(2): 249.

287419

2(*R*)-Hydroxy-2-[2(*S*)-hydroxy-4(*S*),5(*S*)-dimethoxy-3(*S*),5(*S*)-dimethyl-6(*S*)-[4(*R*),4'(*R*)-dimethoxy-3(*R*),3'(*R*),5'(*R*)-trimethyl-5'-[5(*R*)-[5(*R*)-[2(*S*)-hydroxy-4(*S*)-(cyclohexylcarbonyloxy)-2,3(*R*),5(*S*)-trimethyltetrahydropyran-6(*S*)-yl]tetrahydrofuran-2(*R*)-yl]tetrahydrofuran-2(*R*)-yl]spiro[tetrahydropyran-2,2'-tetrahydrofuran]-6(*S*)-ylmethyl]tetrahydropyran-2-yl]acetic acid sodium salt



C48 H79 Na O17; Mol wt: 951.1251

ACTION – Antibacterial, antiprotozoal and antiparasitic agent proven active against the nematode *Nippostrongylus brasiliensis* (IC₅₀ = 1.3 µg/ml), *Eimeria tenella* (MEC [minimal effective concentration] = 0.02 µg/ml,) and *Staphylococcus aureus* 209P (MIC = 0.39 µg/ml). No mortality was observed following single doses of 200-800 mg/kg p.o in mice. A representative compound from a series of polyether derivatives.

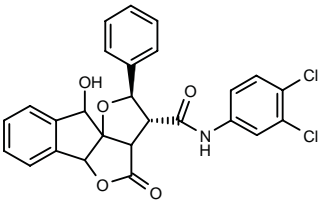
SOURCE – Fujisawa.

REFERENCES

1. Yamamura, A. and Hara, T. (Fujisawa Pharmaceutical Co., Ltd.) *Polyethers cpd., its preparation method, and medicinal compsns. containing it*. JP 2000063395.

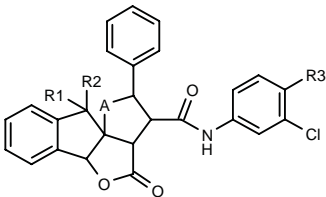
287864

trans-*N*-(3,4-Dichlorophenyl)-10-hydroxy-4-oxo-2-phenyl-2,3,3a,4,5a,10-hexahydrofuro[2,3-*c*]indeno[1,2-*b*]furan-3-carboxamide isomer A



C26 H19 Cl2 N O5; Mol wt: 496.3441

ACTION – Antimicrobial agent that acts by inhibiting aminoacyl-tRNA synthetases and is reported to be active against bacteria including both Gram-positive and Gram-negative aerobic and anaerobic bacteria, mycobacteria, intracellular microbes such as *Chlamydia* and *Rickettsia*, *Mycoplasma* and fungi including *Aspergillus*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Epidermophyton*, *Histoplasma*, *Microsporium*, *Paracoccidioides*, *Pneumocystis*, *Trichophyton* and *Trichosporon*. Compound was shown to inhibit enzyme from *Enterococcus faecalis* PheRS with an IC₅₀ of 0.17 µM and exhibited an MIC value of 3.1 µg/ml against *Staphylococcus aureus* Other compounds from this series of tetracyclic heterocycles include the following:



Compound	R1	R2	R3	A	Isomer	Formula
287866	OH	H	Cl	O	trans B	C ₂₆ H ₁₉ Cl ₂ NO ₅
287868		-O-	Cl	O	trans	C ₂₆ H ₁₇ Cl ₂ NO ₅
287869	OH	H	Cl	NH	A	C ₂₆ H ₂₀ Cl ₂ N ₂ O ₄
287870	OH	H	Cl	NH	B	C ₂₆ H ₂₀ Cl ₂ N ₂ O ₄
287871	OH	H	Cl	NH	C	C ₂₆ H ₂₀ Cl ₂ N ₂ O ₄
287872	OH	H	Me	O	trans A	C ₂₇ H ₂₂ ClNO ₅
287873	OH	H	Me	O	trans B	C ₂₇ H ₂₂ ClNO ₅
288832	OH	H	Me	O	cis	C ₂₇ H ₂₂ ClNO ₅

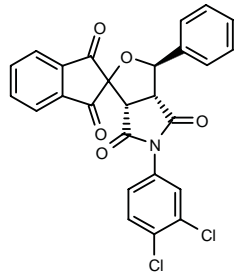
SOURCE – Cubist Pharmaceuticals.

REFERENCES

1. Finn, J. et al. (Cubist Pharmaceuticals, Inc.) *Tetracyclic heterocycles as antimicrobial agents*. WO 0017206.

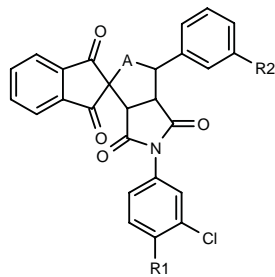
288177

(3' *R*, 3' *aR*, 6' *aS*)-5'-(3,4-Dichlorophenyl)-3'-phenyl-spiro[indane-2,1'-perhydrofuro[3,4-*c*]pyrrole]-1,3,4',6'-tetraone

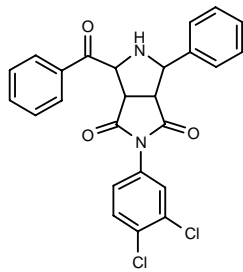


C26 H15 Cl2 N O5; Mol wt: 492.3125

ACTION – Antimicrobial agent proven to inhibit aminoacyl-tRNA synthetases ($IC_{50} = 0.004 \mu M$ against tRNA synthetase from *Staphylococcus aureus*) and to be active against bacteria or fungi, showing an MIC value of 100 $\mu g/ml$ against *S. aureus*. Other exemplified condensed imidazolidinones are:



Compound	R1	R2	A	Isomer	Formula
288178	Cl	H	O	3'R,3'aS,6'aR	C ₂₆ H ₁₅ Cl ₂ NO ₅
288179	Cl	H	NH	3'R,3'aR,6'aS	C ₂₆ H ₁₆ Cl ₂ N ₂ O ₄
288183	Me	Me	O		C ₂₇ H ₁₈ ClNO ₅



288180: C25 H18 Cl2 N2 O3

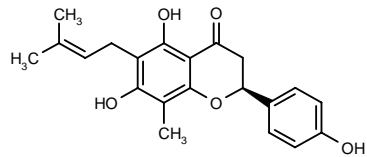
SOURCE – Cubist Pharmaceuticals.

REFERENCES

1. Finn, J. et al. (Cubist Pharmaceuticals, Inc.) *Condensed imidazolidinones as tRNA synthetase inhibitors*. WO 0018772.

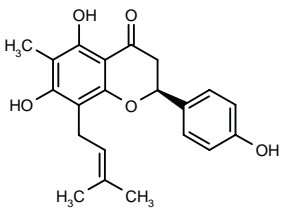
288429

5,7-Dihydroxy-2(*S*)-(4-hydroxyphenyl)-8-methyl-6-(3-methyl-2-butenyl)-3,4-dihydro-2*H*-1-benzopyran-4-one



C21 H22 O5; Mol wt: 354.3998

ACTION – Antibacterial and antifungal flavanone isolated from the aerial parts of the desert legume *Eysenhardtia texana*, found to inhibit the growth of *Staphylococcus aureus in vitro* at 0.1 mg/ml and the growth of *Candida albicans* in an agar diffusion assay. Another flavanone from the same source is:



288430: C21 H22 O5

SOURCE – Research Development Foundation.

REFERENCES

1. Hoffmann, J.J. et al. (Research Development Foundation) *Antibacterial and antifungal flavanones from Eysenhardtia texana*. WO 0020406.

CLAVANIN E(3-23)

287394

H-L-Lys-L-Leu-L-Leu-Gly-L-Lys-L-Ile-L-Ile-L-His-L-His-L-Val-Gly-L-Asn-L-Phe-L-Val-L-His-Gly-L-Phe-L-Ser-L-His-L-Val-L-Phe-OH

C115 H172 N32 O24; Mol wt: 2386.8240

ACTION – Antimicrobial peptide effective against a broad spectrum of microorganisms including group B *Streptococcus*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Listeria monocytogenes*. Compound was also shown to enhance the activity of PG-1 against certain bacteria *in vitro*. Another compound from this series of clavanin peptides is:

H-L-Val-L-Phe-L-Gln-L-Phe-L-Leu-Gly-L-Lys-L-Ile-L-Ile-L-Lys-L-Lys-L-Val-Gly-L-Asn-L-Phe-L-Val-L-Lys-Gly-L-Phe-L-Ser-L-Lys-L-Val-L-Phe-OH

Clavanin A(K) [287395]: C131 H204 N30 O27

SOURCE – University of California, Los Angeles, Los Angeles, CA (US).

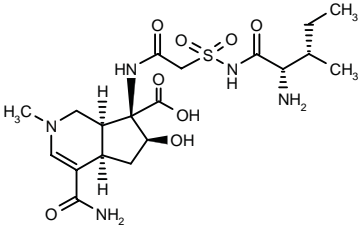
REFERENCES

1. Lehrer, R.I. et al. (University of California, Los Angeles) *Clavanins*. US 6040293.

SB-203207

288511

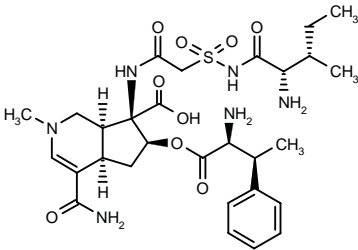
(4a*R*,6*S*,7*R*,7a*S*)-7-[2-[(2*S*,3*S*)-2-Amino-3-methyl-pentanoylamino]sulfonyl]acetamido]-4-(carbamoyl)-6-hydroxy-2-methyl-2,4a,5,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridine-7-carboxylic acid



C19 H31 N5 O8 S; Mol wt: 489.5469

Colorless powder.

ACTION – Antibacterial substance detected in the culture of *Streptomyces* sp. NCIMB 40513. Compound exhibited potent and competitive inhibitory activity against isoleucyl-tRNA synthetase (isoleucine-tRNA ligase) from *Staphylococcus aureus* Oxford, *Pseudomonas fluorescens* NCIB 10586 and *Candida albicans* 3153A (IC₅₀ = 1.7, 1.4 and 1.8 nM, respectively). Despite its high activity against the *S. aureus* Oxford enzyme, no whole-cell activity was detected, which may reflect poor penetration through the staphylococcal cell wall. Weak activity and a limited spectrum were seen with compound against both Gram-positive and Gram-negative bacteria. This compound appears to be a degradation product of **SB-203208**.



SB-203208 [288512]: C29 H42 N6 O9 S

SOURCE – SmithKline Beecham.

REFERENCES

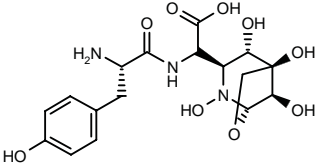
1. Houge-Frydrych, C.S.V. et al. *SB-203207 and SB-203208, two novel isoleucyl tRNA synthetase inhibitors from a Streptomyces sp. II. Structure determination.* J Antibiot 2000, 53(4): 364.

2. Stefanska, A.L. et al. *SB-203207 and SB-203208, two novel isoleucyl tRNA synthetase inhibitors from a Streptomyces sp. I. Fermentation, isolation and properties.* J Antibiot 2000, 53(4): 357.

SB-219383

288509

2(*S*)-(L-Tyrosylamino)-2-[(1*S**,3*S**,4*S**,5*S**,8*R**)-2,4,5,8-tetrahydroxy-7-oxa-2-azabicyclo[3.2.1]oct-3-yl]acetic acid



C17 H23 N3 O9; Mol wt: 413.3807

ACTION – Potent time-dependent and reversible inhibitor of *Staphylococcus aureus* tyrosyl-tRNA synthetase (tyrosine-tRNA ligase; IC₅₀ = 0.6 nM) extracted from *Micromonospora* sp. NCIMB 40684. Despite its high potency against the enzyme, compound showed no whole-cell antibacterial activity against *S. aureus* (MIC > 64 µg/ml) and only weak activity against some *Streptococcus strains* (MIC > 32 µg/ml), probably due to its poor penetration through the cell wall.

SOURCE – SmithKline Beecham.

REFERENCES

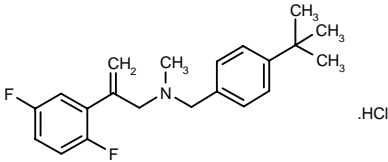
1. Houge-Frydrych, C.S.V. et al. *SB-219383, a novel tyrosyl tRNA synthetase inhibitor from a Micromonospora sp. II. Structure determination.* J Antibiot 2000, 53(4): 351.

2. Stefanska, A.L. et al. *SB-219383, a novel tyrosyl tRNA synthetase inhibitor from a Micromonospora sp. I. Fermentation, isolation and properties.* J Antibiot 2000, 53(4): 345.

ANTIFUNGAL AGENTS

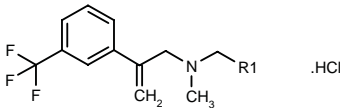
287381

N-(4-*tert*-Butylbenzyl)-*N*-[2-(2,5-difluorophenyl)-2-propenyl]-*N*-methylamine hydrochloride



C21 H25 F2 N . HCl; Mol wt: 365.8924

ACTION – Antifungal agent active *in vitro* against *Trichophyton mentagrophytes* TIMM1189 (MIC = 0.25 µg/ml). Other exemplified compounds include the following:



Compound	R1	Formula
287382	4- <i>t</i> -Bu-Ph	C ₂₂ H ₂₆ F ₃ N.HCl
287383	(<i>E</i>)- <i>t</i> -Bu-ethynylene-CH=CH	C ₂₀ H ₂₄ F ₃ N.HCl

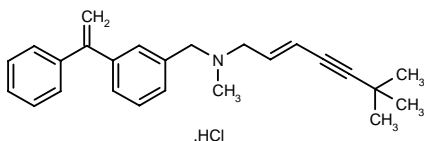
SOURCE – Pola Chemical.

REFERENCES

1. Majima, T. et al. (Pola Chemical Industries Inc.) *Anti-fungal agents and compsns. containing them*. JP 2000053621.

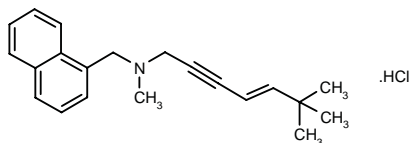
287397

N-(6,6-Dimethylhept-2(*E*)-en-4-ynyl)-*N*-methyl-*N*-[3-(1-phenylvinyl)benzyl]amine hydrochloride

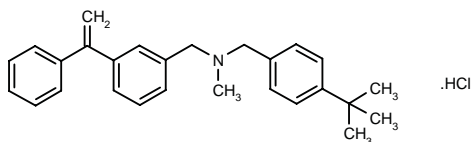


C₂₅ H₂₉ N . HCl ; Mol wt: 379.9720

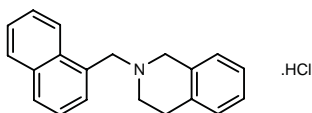
ACTION – Antifungal agent active *in vitro* against *Trichophyton mentagrophytes* TIMM1189 (MIC = 1 µg/ml). Other exemplified compounds from this series of aromatic derivatives include the following:



287398: C₂₁ H₂₅ N . HCl



287399: C₂₇ H₃₁ N . HCl



287400: C₂₀ H₁₉ N . HCl

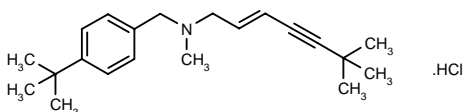
SOURCE – Pola Chemical.

REFERENCES

1. Majima, T. et al. (Pola Chemical Industries Inc.) *Aromatic anti-fungal agents*. JP 2000053619.

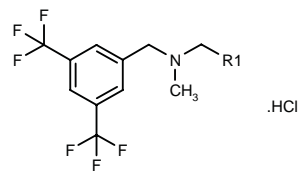
287402

N-(4-*tert*-Butylbenzyl)-*N*-[6,6-dimethylhept-2(*E*)-en-4-ynyl]-*N*-methylamine hydrochloride

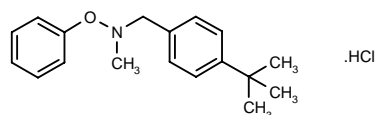


C₂₁ H₃₁ N . HCl; Mol wt: 333.9438

ACTION – Antifungal agent active *in vitro* against *Trichophyton mentagrophytes* TIMM1189 (MIC = 25 µg/ml). Other exemplified compounds from this series of aromatic derivatives include the following:



Compound	R1	Formula
287405	4-t-Bu-Ph	C ₂₁ H ₂₃ F ₆ N.HCl
287406	(<i>E</i>)-t-Bu-ethynylene-CH=CH	C ₁₉ H ₂₁ F ₆ N.HCl



287403: C₁₈ H₂₃ N O . HCl

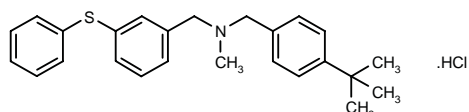
SOURCE – Pola Chemical.

REFERENCES

1. Majima, T. et al. (Pola Chemical Industries Inc.) *Aromatic anti-fungal agents*. JP 2000053620.

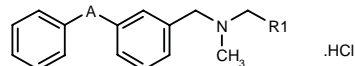
287421

N-(4-*tert*-Butylbenzyl)-*N*-methyl-*N*-[3-(phenylsulfanyl)benzyl]amine hydrochloride



C₂₅ H₂₉ N S . HCl; Mol wt: 412.0380

ACTION – Antifungal agent active *in vitro* against *Trichophyton mentagrophytes* TIMM1189 (MIC = 33 µg/ml). Other compounds from this series of aromatic derivatives include the following:



Compound	R1	A	Formula
287422	(<i>E</i>)-t-Bu-ethynylene-CH=CH	-SO-	C ₂₃ H ₂₇ NOS.HCl
287423	4-t-Bu-Ph	-SO-	C ₂₅ H ₂₉ NOS.HCl
287424	(<i>E</i>)-t-Bu-ethynylene-CH=CH	-S-	C ₂₃ H ₂₇ NS.HCl

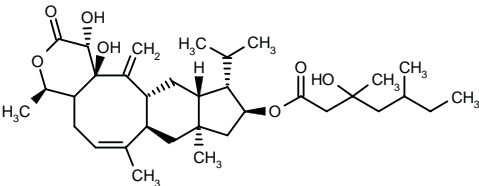
SOURCE – Pola Chemical.

REFERENCES

1. Majima, T. et al. (Pola Chemical Industries Inc.) *Aromatic anti-fungal agents*. JP 2000063348.

287710

3-Hydroxy-3,5-dimethylheptanoic acid (1*R*,4*R*,7*aR*,8*aR*,10*S*,11*S*,11*aR*,12*aR*,13*aR*)-1,13*a*-dihydroxy-4,7,8*a*-trimethyl-11-isopropyl-13-methylene-2-oxo-1,2,4,4*a*,5,7*a*,8,8*a*,9,10,11,11*a*,12,12*a*,13,13*a*-hexadecahydroindeno-[5',6':4,5]cycloocta[1,2-*c*]pyran-10-yl ester



C34 H54 O7; Mol wt: 574.7936

ACTION – Antifungal lactone isolated from the fermentation broth of the microorganism *Codinaea talbotii* FERM BP-6321. The compound inhibited the growth of *Candida albicans* and *Aspergillus fumigatus* with MIC values of < 0.19 µg/ml. No significant cytotoxicity was observed at 5 µg/ml against HepG2 and HeLa cells.

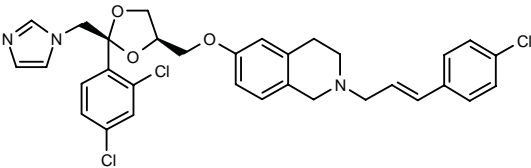
SOURCE – Pfizer.

REFERENCES

1. Kato, Y. et al. (Pfizer Inc.) *An antifungal lactone cpd.*. EP 0989127.

288428

(+)-*cis*-2-[3-(4-Chlorophenyl)-2(*E*)-propenyl]-6-[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]-1,2,3,4-tetrahydroisoquinoline



C32 H30 Cl3 N3 O3; Mol wt: 610.9660

ACTION – Antifungal agent, a specifically claimed compound form a series of 2-(3-phenyl-2-propenyl)-1,2,3,4-tetrahydroisoquinolines with excellent activity against *Candida albicans* in mice when administered at 25 mg/kg p.o. or i.p.; also reported to be active against dermal fungi, e.g., *Trichophyton*.

SOURCE – Aventis Pharma.

REFERENCES

1. Babin, D. et al. (Aventis Pharma SA) *Novel 2-[3-phenyl-2-propenyl]-1,2,3,4-tetrahydroisoquinoline derivs., preparation method and use as fungicides*. EP 0992502, WO 0020413.

XMP-445

288158

D-Lysyl-D-valyl-glycyl-L-tryptophyl-L-leucyl-L-isoleucyl-L-glutaminy-L-leucyl-L-phenylalanyl-L-histidyl-D-lysyl-D-lysine

C74 H117 N19 O14; Mol wt: 1496.8570

ACTION – Peptide derived from domain III of the human bactericidal/permeability-increasing protein (BPI), especially useful as an antifungal agent. XMP-445 was tested against *Candida albicans* SLU-1, *Candida glabrata*, *Cryptococcus neoformans*, *Fusarium solani* and *Aspergillus fumigatus* and gave respective MIC values of 1.0, 4.0, 1.0, 1.0 and 8.0 µg/ml. In mice with systemic *C. albicans* infection, it showed a minimum effective dose of 0.5 mg/kg i.v., which is about one-tenth the maximum tolerated dose. Oral antifungal activity was also demonstrated in mice.

SOURCE – Xoma.

REFERENCES

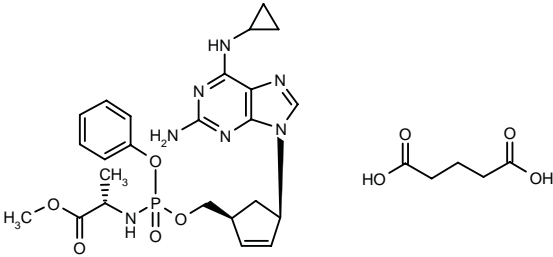
1. Little, R.G. II (Xoma Corp.) *Antifungal and antibacterial peptide*. WO 0018798.

ANTIVIRAL DRUGS

288249

2(*S*)-[[4(*R*)-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]cyclopent-2-en-1(*S*)-ylmethoxy](phenoxy)-phosphorylamino]propionic acid methyl ester glutarate

N-[[4(*R*)-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]cyclopent-2-en-1(*S*)-ylmethoxy](phenoxy)phosphoryl]-L-alanine methyl ester glutarate



C24 H30 N7 O5 P . C5 H8 O4; Mol wt: 659.6332

ACTION – Antiviral agent, a representative compound from a series of phosphoramidate derivatives of abacavir with potent antiviral activity combined with good pharmacokinetic properties and chemical stability. Particularly useful against HIV and/or HBV (hepatitis B virus) infections.

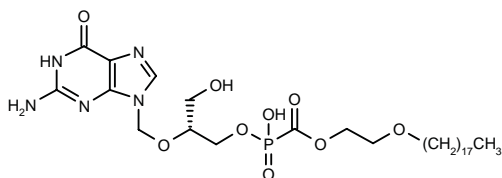
SOURCES – University College Cardiff Consultants; Rega Foundation, Leuven (BE).

REFERENCES

1. McGuigan, C. and Balzarini, J. (University College, Cardiff;Stichting Rega Vzw) *Antiviral purine derivs*. WO 0018775.

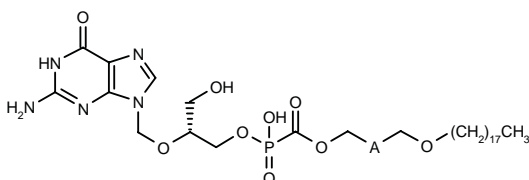
288401

[2(*R*)-(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-ylmethoxy)-3-hydroxypropoxy](hydroxy)phosphorylformic acid 2-(octadecyloxy)ethyl ester



C30 H54 N5 O9 P; Mol wt: 659.7566

ACTION – Antiviral agent, a phospholipid prodrug wherein ganciclovir is coupled with a lipophilic alkoxyalkyl phosphonoformate, proven active *in vitro* in human cytomegalovirus- and HSV-1-infected MRC-5 cells (IC_{50} = 0.21 and 0.004 μ M, respectively). The conjugate has the potential to deliver both ganciclovir and phosphonoformate and is expected to be orally available in animals. Other phospholipid ganciclovir prodrugs are:



Compound	A	Formula
288403	-CH2-	C ₃₁ H ₅₆ N ₅ O ₉ P
288404	-(CH2)2-	C ₃₂ H ₅₈ N ₅ O ₉ P

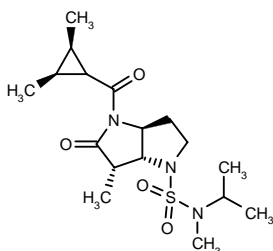
SOURCE – University of California, San Diego, La Jolla, CA (US).

REFERENCES

1. Beadle, J.R. et al. *Phospholipid prodrugs of antiviral nucleosides: Synthesis and activity of octadecyloxyethyl-, propyl and -butyl esters of ganciclovir phosphonoformate*. *Antivir Res* 2000, 46(1): Abst 141.

288439

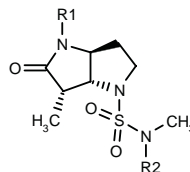
(3*aS*,6*S*,6*aR*)-*N*-Isopropyl-4-(*cis*-2,3-dimethylcyclopropylcarbonyl)-*N*,6-dimethyl-5-oxoperhydropyrrolo-[3,2-*b*]pyrrole-1-sulfonamide



C17 H29 N3 O4 S; Mol wt: 371.4991

ACTION – Antiviral agent particularly useful in the treatment and prophylaxis of infections caused by viruses that encode for a serine protease enzyme, especially those of the herpesvirus family. Compound was shown to inhibit proteases from herpes simplex virus type 1 (HSV-1; 105% inhibition at 0.5 μ M) and human cytomegalovirus (HCMV; IC_{50} = 0.98 and 3.1 μ M, respectively, with or without 15-min preincubation), and exhibited antiviral

activity against HSV-1 and HSV-2 in a plaque reduction assay (IC_{50} = 3.3 and 3.4 μ M, respectively); it was ineffective against varicella-zoster virus (VZV) and CMV (IC_{50} > 50 and > 100 μ M, respectively). Compound exhibited low cytotoxicity against Vero cells (CC_{50} = 315 μ M). A representative compound from a series of pyrrolopyrrolone derivatives, wherein the following are also included:



Compound	R1	R2	Formula
288441	2-benzothiazolyl	CH(Me)Et	C ₁₉ H ₂₆ N ₄ O ₃ S ₂
288442	<i>cis</i> -2,3-(Me)2-cyclopropyl-CO	3-NO2-PhCH2NHCOCH2	C ₂₃ H ₃₁ N ₅ O ₇ S
288443	<i>cis</i> -2,3-(Me)2-cyclopropyl-CO	2,4-(MeO)2-5-NO2-PhCH2NHCOCH2	C ₂₅ H ₃₅ N ₅ O ₉ S

SOURCE – Glaxo Wellcome.

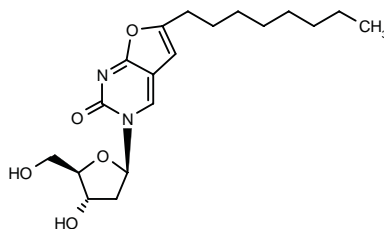
REFERENCES

1. Borthwick, A.D. et al. (Glaxo Group Ltd.) *Pyrrolopyrrolone derivs. as antiviral agents*. WO 0018770.

CF-1368*

282173

3-(2'-Deoxy- β -D-ribofuranosyl)-6-octyl-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one



C19 H28 N2 O5; Mol wt: 364.4392

ACTION – Antiviral agent active against varicella-zoster virus (VZV; EC_{50} = 0.008 and 0.024 μ M, respectively, against OKA and YS strains) and approximately 300-fold more potent than aciclovir; it was completely inactive against herpes simplex virus types 1 and 2 (HSV-1, HSV-2), cytomegalovirus (CMV) and vaccinia virus, and showed no cytotoxicity at up to 200 μ M.

SOURCES – Cardiff University, Cardiff (GB); Rega Institute for Medical Research, Leuven (BE).

REFERENCES

1. McGuigan, C. et al. (University College, Cardiff) *Anti-viral pyrimidine nucleoside analogues*. EP 0980377, WO 9849177.
2. Brancale, A. et al. *Design synthesis and evaluation of new antiviral nucleosides*. *Antivir Res* 2000, 46(1): Abst 128.
3. McGuigan, C. et al. *Potent and selective inhibition of varicella-zoster virus (VZV) by nucleoside analogues with an unusual bicyclic base*. *J Med Chem* 1999, 42(22): 4479.

*Identified compound **282173** Drug Data Rep 2000, 022(02): 0168.

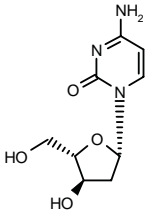
NV-02C

288294

4-Amino-1-[(2*S*,4*R*,5*S*)-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl]pyrimidin-2(1*H*)-one

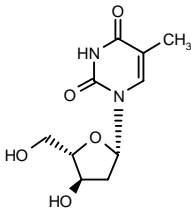
β-L-Deoxycytidine

L-dC



C9 H13 N3 O4; Mol wt: 227.2187

ACTION – Agent for the treatment of hepatitis B virus (HBV) infections (EC₅₀ = 0.05-0.26 μM in 2.2.15 cells), also active against the related woodchuck hepatitis virus (WHV; IC₅₀ = 1.8 μM against WHV DNA polymerase) and duck hepatitis B virus (DHBV; ED₅₀ = 0.05 μM or less in primary duck hepatocytes); compound was not active against a range of DNA or RNA viruses, was not cytotoxic (CC₅₀ > 2000 μM), did not show mitochondrial toxicity, did not inhibit human cellular DNA polymerases and was not mutagenic. It was activated to the 5'-triphosphate forms by cellular kinases, L-dTTP and L-dCTP showing extended intracellular half-lives. In a chronic WHV model, compound at doses of 0.01-10 mg/kg/day p.o. for 28 days induced dose-dependent viral load reductions of up to 8 log from baseline; viral rebound was seen within 1 week following cessation of treatment but no evidence of drug-related toxicity was seen during the 4-week treatment or during 8 weeks of follow-up. A promising clinical candidate for the once-daily oral treatment of HBV. Another compound from this series of β-L-2'-deoxynucleosides is:



NV-02B [288295]: C10 H14 N2 O5
L-dT

SOURCE – Novirio.

REFERENCES

1. Gosselin, G. et al. (Novirio Pharmaceuticals Ltd.;CNRS [Centre National de la Recherche Scientifique]) *β-L-2'-Deoxy-nucleosides for the treatment of hepatitis B*. WO 0009531.

2. Bridges, E.G. et al. *Antiviral activity of β-L-thymidine and β-L-deoxycytidine in the woodchuck model of chronic hepatitis B infection*. Antivir Res 2000, 46(1): Abst 91.

3. Bryant, M.L. et al. *Anti-hepatitis B specific β-L-2'-deoxynucleosides*. Antivir Res 2000, 46(1): Abst 67.

4. Farai, A. et al. *β-L-Thymidine and β-L-2'-deoxycytidine are potent, selective and specific anti-hepatitis B virus agents*. Antivir Res 2000, 46(1): Abst 88.

5. Pierra, C. et al. *β-L-2'-Deoxynucleosides as potent anti-HBV agents (Part II): Large-scale stereospecific syntheses of β-L-2'-deoxycytidine and β-L-thymidine*. Antivir Res 2000, 46(1): Abst 90.

6. Placidi, L. et al. *Cellular pharmacology of β-L-thymidine (L-dT, NV-02B) and β-L-2'-deoxycytidine (L-dC, NV-02C) in HepG2 cells and primary rat, monkey and human hepatocytes*. Antivir Res 2000, 46(1): Abst 70.

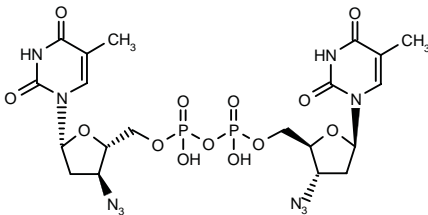
7. *Novirio receives NIAID grant to further R&D of anti-HBV drugs*. DailyDrugNews.com (Daily Essentials) 2000, May 12.

AIDS MEDICINES

287324

Bis(3'-Azido-3'-deoxythymidine) 5',5''-P¹,P²-diphosphate

Di-AZT-pyrophosphate



C20 H26 N10 O13 P2; Mol wt: 676.4304

ACTION – Dinucleoside phosphate prodrug of zidovudine (AZT) proven to be equieffective to AZT in HIV-infected MT-4 cells (IC₅₀ = 0.031 μM vs. 0.028 μM), with even lower cytotoxicity (CC₅₀ > 100 μM vs. 70 μM). This compound is particularly useful as a prodrug for transport by erythrocytes to macrophages, in which the pyrophosphate bond is cleaved to give two nucleotides (AZT monophosphate and AZT itself), which are released at a very slow rate without being substantially inactivated.

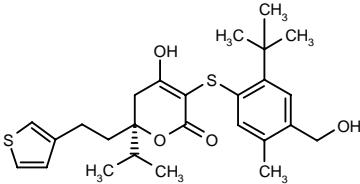
SOURCES – Biosearch Italia; Lepetit.

REFERENCES

1. De Flora, A. et al. (Biosearch Italia SpA;Lepetit SpA) *Dinucleoside-5',5'-pyrophosphates*. US 6040297, WO 9602554.

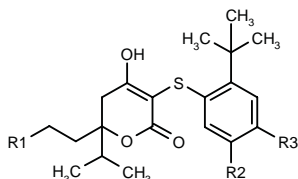
287590

3-[2-*tert*-Butyl-4-(hydroxymethyl)-5-methylphenyl-sulfanyl]-4-hydroxy-6(*S*)-isopropyl-6-[2-(2-thienyl)ethyl]-5,6-dihydro-2*H*-pyran-2-one



C26 H34 O4 S2; Mol wt: 474.6826

ACTION – Potent inhibitor of HIV-1 protease that shows improved pharmacokinetic parameters when compared to known related compounds due to the presence in its structure of fewer peripheral polar groups. It gave a K_i value of 0.07 nM in an HIV protease assay, and it displayed antiviral efficacy ($EC_{50} = 0.14 \mu\text{M}$) and a high therapeutic index ($TC_{50}/EC_{50} = 650$) in HIV-infected CEM cells. In pharmacokinetic studies in animals, this compound showed a clear improvement in C_{max} (95 μM at 25 mg/kg p.o. in mice; 160 μM at 10 mg/kg i.v. in rats) and $t_{1/2}$ (9.5 h and 12.0 h, respectively). Other exemplified dihydropyrones include the following:



Compound	R1	R2	R3	Formula
287591	3-thienyl	Me	CH ₂ OH	C ₂₆ H ₃₄ O ₄ S ₂
287592	2-(CH ₂ OH)-3-thienyl	Me	NH ₂	C ₂₆ H ₃₅ NO ₄ S ₂
287593	2-thiazolyl	Me	CH ₂ OH	C ₂₅ H ₃₃ NO ₄ S ₂
287596	2-(CH ₂ OH)-Ph	-CH=CHNH-		C ₂₉ H ₃₆ NO ₄ S
287597	3-F-Ph	-SC(NH ₂)=N-		C ₂₇ H ₃₁ FN ₂ O ₃ S ₂

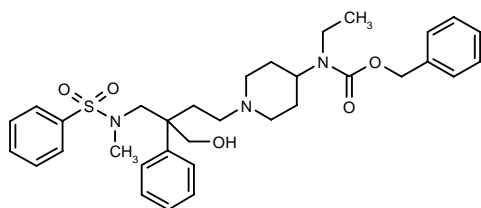
SOURCE – Pfizer.

REFERENCES

- Boyer, F.E. Jr. et al. (Warner-Lambert Co.) *HIV protease inhibitor*. WO 0015634.

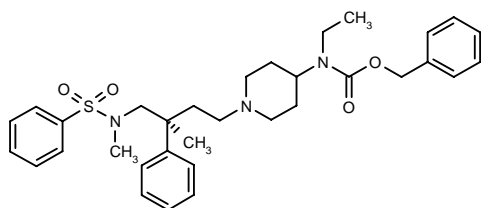
287594

N-Ethyl-*N*-[1-[4-hydroxy-3-(*N*-methylphenylsulfonamido-methyl)-3-phenylbutyl]piperidin-4-yl]carbamic acid benzyl ester enantiomer A



C33 H43 N3 O5 S; Mol wt: 593.7847

ACTION – Anti-HIV-1 agent, a CCR5 receptor antagonist ($IC_{50} = 0.8 \text{ nM}$) with submicromolar activity against HIV-1 replication in peripheral blood mononuclear cells ($IC_{95} = 94\text{--}188 \text{ nM}$). Another related compound is:



287595: C33 H43 N3 O4 S

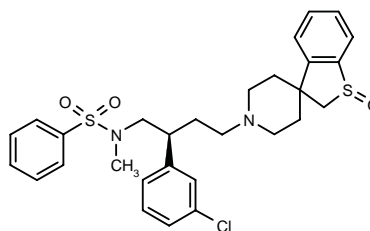
SOURCE – Merck & Co.

REFERENCES

- Caldwell, C.G. et al. (Merck & Co., Inc.) *Cyclic amine modulators of chemokine receptor activity*. EP 1003514, WO 9904794.
- Cladwell, C.G. et al. *Discovery of potent human CCR5 antagonists for the treatment of HIV-1 infection-IV*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 120.

287839

N-[2(*S*)-(3-Chlorophenyl)-4-[1-oxospiro[benzo[*b*]thio-phen-3(2*H*),4'-piperidin-1'-yl]butyl]-*N*-methylbenzene-sulfonamide



C29 H33 Cl N2 O3 S2; Mol wt: 557.1757

ACTION – Potent human chemokine CCR5 receptor antagonist ($IC_{50} = 10 \text{ nM}$) with antiviral activity against HIV-1 ($IC_{95} = 1.5 \mu\text{M}$).

SOURCE – Merck & Co.

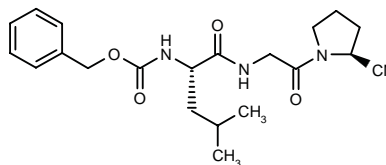
REFERENCES

- Mills, S.G. et al. (Merck & Co., Inc.) *Spiro-subst. azacycles as modulators of chemokine receptor activity*. US 5962462, WO 9825605.
- Meurer, L.C. et al. *Discovery of potent human CCR5 antagonists for the treatment of HIV-1 infection*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 118.

TREATMENT OF PROTOZOAL DISEASES

287259

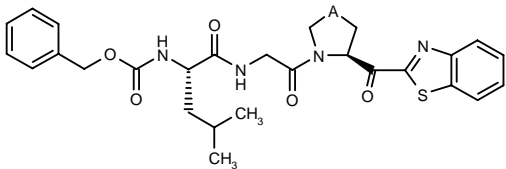
1-[*N*-(Benzyloxycarbonyl)-L-leucyl-glycyl]pyrrolidine-2(*S*)-carbonitrile



C21 H28 N4 O4; Mol wt: 400.4762

Amorphous solid, m.p. 57-9 °C; $[\alpha]_D^{20} -82.9^\circ$ (c 2.6, CH₂Cl₂).

ACTION – Antitrypanosomal agent, a potent, reversible and competitive inhibitor of Tc80 proteinase from *Trypanosoma cruzi* ($IC_{50} = 52 \text{ nM}$; $K_i = 38 \text{ nM}$) potentially useful for the treatment of Chagas' disease.



Compound	A	Formula
287257	CH2	C ₂₈ H ₃₂ N ₄ O ₅ S
287258	S	C ₂₇ H ₃₀ N ₄ O ₅ S ₂

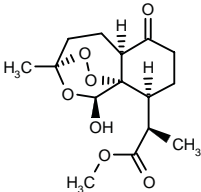
SOURCES – Universidade de Brasilia, Brasilia (BR); CNRS.

REFERENCES

1. Joyeau, R. et al. *Synthesis and activity of pyrrolidinyl- and thiazolidinyl-dipeptide derivatives as inhibitors of the Tc80 prolyl oligopeptidase from Trypanosoma cruzi*. Eur J Med Chem 2000, 35(2): 257.

287734

2(R)-[(3R,5aR,9S,9aS,10S)-10-Hydroxy-3-methyl-6-oxo-3,9a-(epoxymethano)-3,4,5,5a,6,7,8,9-octahydro-1,2-benzodioxepin-9-yl]propionic acid methyl ester



C15 H22 O7; Mol wt: 314.3318

ACTION – Artemisinin analogue with good *in vitro* anti-malarial activity (EC₅₀ = 39 nM) and high selectivity.

SOURCES – Okayama University, Okayama (JP); Tohoku University, Sendai (JP).

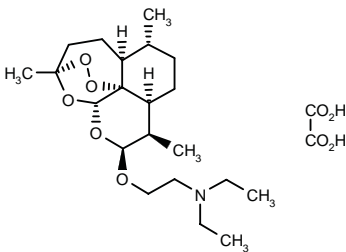
REFERENCES

1. Takasu, K. et al. *Synthesis and antimalarial activity of artemisinin analogs*. 120th Annu Meet Pharm Soc Jpn (March 29-31, Gifu) 2000, Abst 30-PB-12-50.

288069

N,N-Diethyl-N-[2-[(3R,5aS,6R,8aS,9R,10S,12R,12aR)-3,6,9-trimethylperhydro-3,12-epoxypyran[4,3-]]-1,2-benzodioxepin-10-yloxy]ethyl]amine oxalate

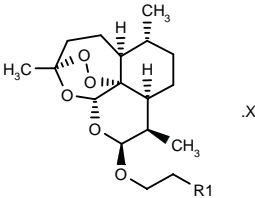
10β-[2-(N,N-Diethylamino)ethyl]-10-deoxoartemisinin oxalate



C21 H37 N O5 . C2 H2 O4; Mol wt: 473.5591

M.p. 100-2 °C.

ACTION – Antimalarial agent, a derivative of artemisinin with the ability to protect mice from *Plasmodium berghei* (K173 strain) infection (ED₅₀ = 1.74 and 27.66 mg/kg/day p.o. and s.c., respectively) with an efficacy superior to artesunic acid (ED₅₀ = 6.33 mg/kg/day p.o.). In *Plasmodium knowlesi*-infected rhesus monkeys, compound was shown to reduce parasites more rapidly than artesunic acid, but at a dose of 3.16 mg/kg it did not cleanse all parasites, in contrast to artesunic acid. Other related compounds include the following:



Compound	R1	X	Formula
288068	N(Me)2	oxalate	C ₁₉ H ₃₃ NO ₅ .C ₂ H ₂ O ₄
288070	4-morpholinyl-CH2	maleate	C ₂₂ H ₃₇ NO ₆ .C ₄ H ₄ O ₄

SOURCES – Academy of Military Medical Sciences, Beijing (CN); Shanghai Institute Materia Medica, Shanghai (CN).

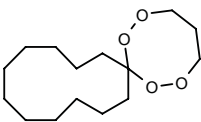
REFERENCES

1. Li, Y. and Wu, S.X. (Shanghai Institute Materia Medica) *Synthesis of a nitrogen-containing derivative of a compound isolated from Artemisia annua L*. CN 1052673.
2. Li, Y. et al. *Synthesis and antimalarial activity of artemisinin derivatives containing an amino group*. J Med Chem 2000, 43(9): 1635.

N-89

287732

1,2,6,7-Tetraoxaspiro[7.11]nonadecane



C15 H28 O4; Mol wt: 272.3822

ACTION – Antimalarial agent with potent *in vitro* activity against *Plasmodium falciparum* (EC₅₀ = 10 nM) and the ability to overcome chloroquine resistance. In mice infected with *Plasmodium berghei* NK65, compound also showed potent antimalarial activity (ED₅₀ = 12 mg/kg/day i.p. and 20 mg/kg/day p.o. for 4 days) and low acute toxicity (LD₅₀ > 1600 mg/kg). When compound was administered orally at a dose of 160 mg/kg/day for 3 days, complete cure was obtained in 80% of treated mice.

SOURCES – Okayama University, Okayama (JP); Osaka University, Osaka (JP).

REFERENCES

1. Ishizuka, Y. et al. *Development of novel antimalarial agents. I. Antimalarial effect of cyclic peroxide*. 120th Annu Meet Pharm Soc Jpn (March 29-31, Gifu) 2000, Abst 30-PB-10-63.

2. Nagai, Y. et al. *Development of novel antimalarial agents. II. Antimalarial effect of cyclic peroxide*. 120th Annu Meet Pharm Soc Jpn (March 29-31, Gifu) 2000, Abst 30-PB-10-62.

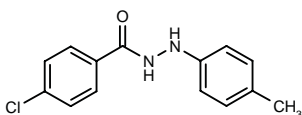
3. Tsuchiya, K. et al. *Synthesis, crystal structure and anti-malarial activity of novel spiro-1,2,4,5-tetraoxacycloalkanes*. Tetrahedron Lett 1999, 40(21): 4077.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

274089

4-Chloro-*N'*-(4-methylphenyl)benzohydrazide



C14 H13 Cl N2 O; Mol wt: 260.7227

ACTION – Potential antiinflammatory agent with selective inhibitory activity against cyclooxygenase type 2 (COX-2; IC₅₀ = 10 nM) versus COX-1 (IC₅₀ > 10 μM).

SOURCE – R.W. Johnson.

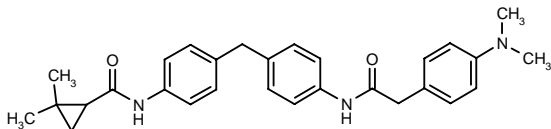
REFERENCES

1. Sui, Z. et al. *1,3-Diarylcycloalkano-[1,2-d]-pyrazoles and diphenyl hydrazides as selective inhibitors of cyclooxygenase-2*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 202.

2. Sui, Z. et al. *1,3-Diarylcycloalkanopyrazoles and diphenyl hydrazides as selective inhibitors of cyclooxygenase-2*. Bioorg Med Chem Lett 2000, 10(6): Abst 601.

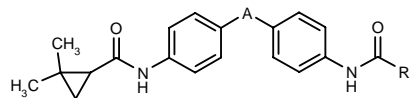
287627

N-[4-[4-[2-[4-(Dimethylamino)phenyl]acetamido]benzyl]phenyl]-2,2-dimethylcyclopropanecarboxamide



C29 H33 N3 O2; Mol wt: 455.5987

ACTION – An inhibitor of AP-1 and NF-κB activation, also reported to inhibit inflammatory cytokine production, matrix metalloproteinases and cell adhesion factor expression, with potential as an antiinflammatory, antirheumatic, immunosuppressive and antimetastatic agent, as well as for the treatment of arteriosclerosis and viral infections. *In vitro*, compound inhibited IL-1β-stimulated NF-κB activity in human umbilical vein endothelial cells (HUVEC) with an IC₅₀ of 0.03 μg/ml. Other compounds from this series of benzene derivatives include the following:



Compound	R1	A	Isomer	Formula
287628	2,2-(Me)2-1-cyclopropyl	-S-		C ₂₄ H ₂₈ N ₂ O ₂ S
287629	2,2-(Me)2-1(R)-cyclopropyl	-CH(OH)-	1S	C ₂₅ H ₃₀ N ₂ O ₃
287631	2-pyrrolidinyl	-CH ₂ -		C ₂₄ H ₂₉ N ₃ O ₂
287633	4-MeO-Ph(CH ₂) ₃	-CH ₂ -		C ₃₀ H ₃₄ N ₂ O ₃

SOURCE – Ajinomoto.

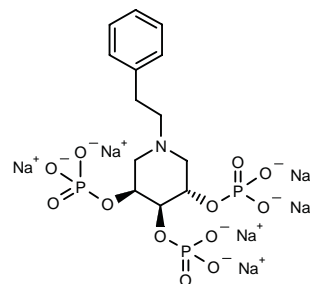
REFERENCES

1. Iino, Y. et al. (Ajinomoto Co., Inc.) *Benzene derivs. and medicinal use thereof*. WO 0015603.

287723

Phosphoric acid 1-(2-phenylethyl)-3(*S*),5(*S*)-bis(phosphonoxy)piperidin-4-yl ester hexasodium salt

1-(2-Phenylethyl)-3(*S*),4,5(*S*)-tris(phosphonoxy)-piperidine hexasodium salt



C13 H16 N Na6 O12 P3; Mol wt: 609.1264

ACTION – Antiinflammatory agent proven active in the carrageenan-induced paw edema model in mice, producing 27% inhibition of paw weight at 64 mg/kg i.v. It exhibited a good safety profile in the Irwin test at doses up to 512 mg/kg i.v. in mice.

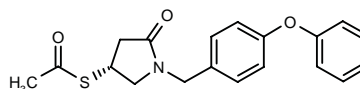
SOURCE – Perstorp Pharma.

REFERENCES

1. Persson, L. and Rehnberg, N. (Perstorp Pharma) *Heterocyclic chemical cpd*. US 6046334, WO 9718220.

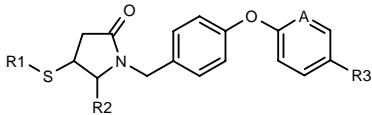
287789

Thioacetic acid *S*-[5-oxo-1-[4-(phenoxybenzyl)pyrrolidin-3(*R*)-yl] thioester



C19 H19 N O3 S; Mol wt: 341.4291

ACTION – An inhibitor of matrix metalloproteinases such as MMP-13 (collagenase 3; IC₅₀ = 0.009 μM against human recombinant enzyme) that was found to be effective in inhibiting cartilage collagen degradation induced by human recombinant IL-1β (91% inhibition at 1 μM). Within this series of thiol derivatives, the following are also included:



Compound	R1	R2	R3	A	Isomer	Formula
287793	H	H	H	CH	R	C ₁₇ H ₁₇ NO ₂ S
287797	H	CH ₂ OCH ₂ Ph	H	CH		C ₂₅ H ₂₅ NO ₃ S
287798	H	H	Cl	CH		C ₁₇ H ₁₆ ClNO ₂ S
287799	Ac	H	H	N		C ₁₈ H ₁₈ N ₂ O ₃ S

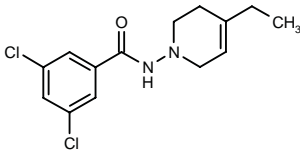
SOURCE – Takeda.

REFERENCES

1. Yamashita, T. et al. (Takeda Chemical Industries, Ltd.) *Novel thiol derivs., process for producing the same and utilization thereof.* WO 0017162.

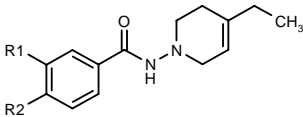
287790

3,5-Dichloro-*N*-(4-ethyl-1,2,3,6-tetrahydropyridin-1-yl)-benzamide



C14 H16 Cl2 N2 O; Mol wt: 299.1994

ACTION – Nonsteroidal antiinflammatory agent proven to inhibit nitric oxide (NO) generation (IC₅₀ = 1 μM) and inducible NO synthase (iNOS) activity in RAW 264.7 macrophages stimulated with lipopolysaccharide. Within this series of substituted tetrahydropyridines the following are also included:



Compound	R1	R2	Formula
287791	H	Br	C ₁₄ H ₁₇ BrN ₂ O
287792	CF ₃	H	C ₁₅ H ₁₇ F ₃ N ₂ O
287794	H	Bu	C ₁₈ H ₂₆ N ₂ O
287795	OMe	H	C ₁₅ H ₂₀ N ₂ O ₂
287796	H	Et	C ₁₆ H ₂₂ N ₂ O

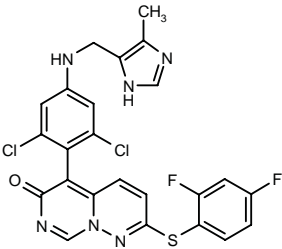
SOURCE – Florida A&M University, Tallahassee, FL (US).

REFERENCES

1. Yoon, K.J. et al. *The effect of novel non-steroidal anti-inflammatory agent on nitric oxide generation and iNOS activity in RAW 264.7 macrophages.* FASEB J 2000, 14(4): Abst 142.9.

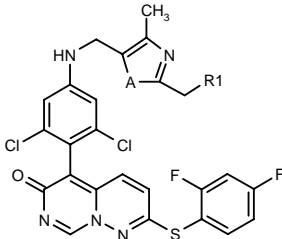
287885

5-[2,6-Dichloro-4-(4-methyl-1*H*-imidazol-5-ylmethyl-amino)phenyl]-2-(2,4-difluorophenylsulfanyl)-6*H*-pyrido[1,6-*b*]pyridazin-6-one



C24 H16 Cl2 F2 N6 O S; Mol wt: 545.3994

ACTION – Mitogen-activated protein (MAP) kinase p38 inhibitor, expected to be of use in the treatment of disorders associated with IL-1, IL-6, IL-8 and TNF over-production including cancer, inflammatory and autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases such as sepsis and septic shock, viral diseases and neurodegenerative disorders. Other exemplified compounds include the following:



Compound	R1	A	Formula
287886	Me	NH	C ₂₆ H ₂₀ Cl ₂ F ₂ N ₆ OS
287887	H	S	C ₂₅ H ₁₇ Cl ₂ F ₂ N ₅ OS ₂
287888	H	N(Me)	C ₂₆ H ₂₀ Cl ₂ F ₂ N ₆ OS

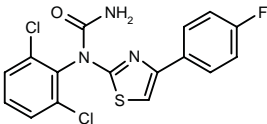
SOURCE – Vertex.

REFERENCES

1. Salituro, F. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of p38.* WO 0017204.

287892

N'-(2,6-Dichlorophenyl)-*N*'-[4-(4-fluorophenyl)thiazol-2-yl]urea



C16 H10 Cl2 F N3 O S; Mol wt: 382.2450

ACTION – Mitogen-activated protein (MAP) kinase p38 inhibitor, expected to be of use in the treatment of disorders associated with IL-1, IL-6, IL-8 and TNF overproduction including cancer, inflammatory and autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases such as sepsis and septic shock, viral diseases and neurodegenerative disorders.

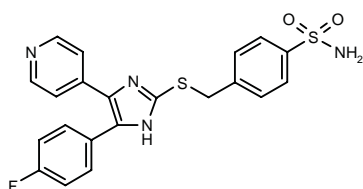
SOURCE – Vertex.

REFERENCES

1. Salituro, F. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of p38*. WO 0017175.

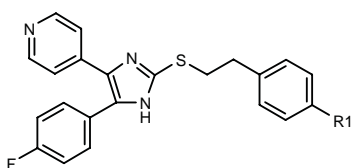
288024

4-[5-(4-Fluorophenyl)-4-(4-pyridyl)-1*H*-imidazol-2-ylsulfonylmethyl]benzenesulfonamide



C21 H17 F N4 O2 S2; Mol wt: 440.5213

ACTION – Antiinflammatory agent that acts by inhibiting the release of cytokines, as well as the arachidonic acid cascade; *in vitro*, compound inhibited cyclooxygenase type 1 (COX-1) and type 2 (COX-2) and 5-lipoxygenase (5-LO), as well as lipopolysaccharide (LPS)-stimulated TNF- α and IL-1 β release from human peripheral blood mononuclear cells, with respective IC₅₀ values of 0.038, 10.0, 2.8, 3.1 and 18 μ mol. Other specifically claimed compounds from this series of 2-arylalkylthio-, 2-arylalkenylthio- and 2-arylalkinylthio-imidazoles include the following:



Compound	R1	Formula
288025	SO2NH2	C ₂₂ H ₁₉ FN ₄ O ₂ S ₂
288026	SMe	C ₂₃ H ₂₀ FN ₃ S ₂

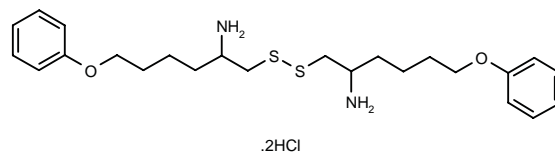
SOURCE – Merckle.

REFERENCES

1. Laufer, S. et al. (Merckle GmbH) *2-Aylthio-imidazoles, 2-arylalkenyl-thio-imidazoles and 2-arylalkinyl-thio-imidazoles as anti-inflammatory substances and substances inhibiting the release of cytokine*. DE 19842833, WO 0017192.

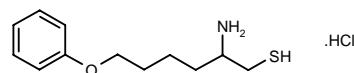
288034

Bis(2-amino-6-phenoxyhexyl)disulfide dihydrochloride



C24 H36 N2 O2 S2 . 2HCl; Mol wt: 521.6142

ACTION – Antiinflammatory agent, an LTA₄ hydrolase inhibitor that exhibits potent antiarthritic activity in a collagen-induced arthritis model in rats at 10 mg/kg i.p., being more potent than indomethacin at 1.5 mg/kg p.o. Compound is reported to act as a prodrug of **288035**, which was found to inhibit zymosan-induced paw edema in mice (35% inhibition at 30 mg/kg p.o.), as well as to inhibit the increase in LTB₄ levels induced by carrageenan in a murine air pouch model (24% inhibition at 25 mg/kg p.o.).



288035: C12 H19 N O S . HCl

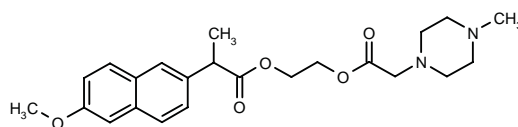
SOURCES – Bioprojet; INSERM, Paris Cedex (FR).

REFERENCES

1. Danvy, D. et al. (Societe Civile Bioprojet;INSERM [Institut National de la Sante et de la Recherche Medicale]) *LTA4 hydrolase inhibitors*. FR 2783518, WO 0017133.

288063

2-(6-Methoxy-2-naphthyl)propionic acid 2-[2-(4-methyl-1-piperazinyl)acetoxy]ethyl ester



C23 H30 N2 O5; Mol wt: 414.4990

ACTION – Antiinflammatory agent, a prodrug of naproxen with improved aqueous solubility at pH 5.0 and lipophilicity at pH 7.4. Compound was rapidly converted to the parent drug in human serum and showed a high permeability coefficient through human skin, with a 4- and 1.5-fold increase in skin permeation compared to naproxen at pH 7.4 and 5.0, respectively. Potentially useful as a topical antiinflammatory agent for the treatment of local soft tissue and joint inflammation.

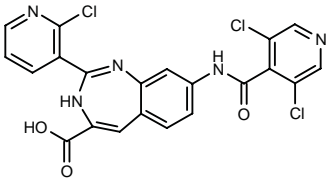
SOURCE – University of Kuopio, Kuopio (FI).

REFERENCES

1. Rautio, J. et al. *Synthesis and in vitro evaluation of novel morpholinyl- and methylpiperazinylacyloxyalkyl prodrugs of 2-(6-methoxy-2-naphthyl)propionic acid (naproxen) for topical drug delivery*. J Med Chem 2000, 43(8): 1489.

288094

2-(2-Chloropyridin-3-yl)-8-(3,5-dichloropyridin-4-ylcarbox-amido)-3*H*-1,3-benzodiazepine-4-carboxylic acid



C21 H12 Cl3 N5 O3; Mol wt: 488.7168

ACTION – Cell adhesion modulator that selectively inhibits the α_4 subgroup of integrins ($\alpha_4\beta_1$ and $\alpha_4\beta_7$), and is thus particularly useful for the treatment of immune and inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses, asthma and inflammatory bowel disease.

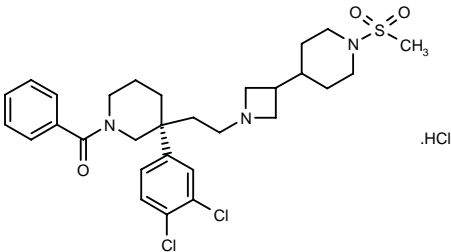
SOURCE – Celltech Group.

REFERENCES

1. Brown, J.A. et al. (Celltech Chiroscience plc) *1,3-Benzodiazepines with integrin inhibitory activity for use in the treatment of inflammatory disorders*. WO 0018760.

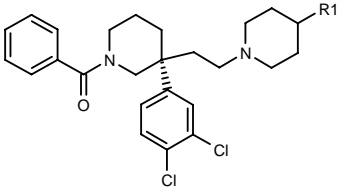
288095

1-[3(*S*)-(3,4-dichlorophenyl)-3-[2-[3-[1-(methylsulfonyl)piperidin-4-yl]azetidin-1-yl]ethyl]piperidin-1-yl]-1-phenylmethanone hydrochloride



C29 H37 Cl2 N3 O3 S . HCl; Mol wt: 615.0622

ACTION – Tachykinin antagonist with selectivity for NK₂ receptors and reported to exhibit increased metabolic stability as compared to previously described structurally related compounds. *In vitro*, compound exhibited a pK_i value of 8.3 for human NK₂ receptors cloned in CHO cells, as compared to a pK_i value of 7.4 for guinea pig cortical NK₃ receptors. In addition, it exhibited a t_{1/2} of 53 min when incubated in human hepatic microsomes. Potentially useful in the treatment of arthritis, psoriasis, asthma, inflammatory bowel disease, anxiety, depression, dementia, psychosis, irritable bowel syndrome, gastro-esophageal reflux, colitis, Crohn's disease, incontinence, chronic obstructive airways disease, eczema, contact dermatitis, rhinitis, hypersensitivity disorders, peripheral neuropathy, cough and acute or chronic pain. Other compounds from this series of substituted benzoylpiperidine derivatives include the following:



Compound	R1	Formula
288096	4-THP	C ₃₀ H ₃₈ Cl ₂ N ₂ O ₂
288105	1-(MeSO ₂)-3-azetidinyl	C ₂₉ H ₃₇ Cl ₂ N ₃ O ₃ S

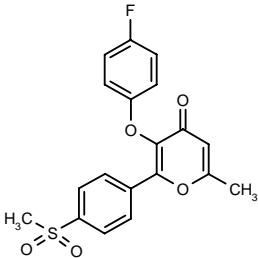
SOURCE – Pfizer.

REFERENCES

1. Fox, D.N.A. (Pfizer Inc.;Pfizer Ltd.) *Substd. benzoylpiperidine derivs. and their use as neurokinin antagonists*. EP 0992493, JP 2000119251.

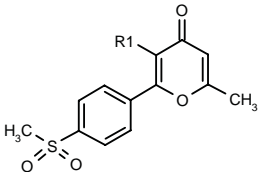
288120

3-(4-Fluorophenoxy)-6-methyl-2-[4-(methylsulfonyl)phenyl]-4*H*-pyran-4-one



C19 H15 F O5 S; Mol wt: 374.3865

ACTION – Potent and selective cyclooxygenase type 2 (COX-2) inhibitor with potential for the treatment of COX-2-mediated disorders such as inflammation, pain, fever and asthma. *In vitro*, compound exhibited IC₅₀ values of 0.96 and > 100 μ M, respectively, for COX-2 and COX-1 in human whole blood. In addition, compound displayed potent activity in the adjuvant-induced arthritis model in rats, giving 75% inhibition at 1 mg/kg/day p.o. x 7 days, as compared to 64% inhibition for indomethacin at the same dose, while having the advantage over indomethacin of being devoid of ulcerogenic activity in this species at doses as high as 100 mg/kg. Other exemplified compounds from this series of 2-phenylpyran-4-one derivatives include the following:



Compound	R1	Formula
288121	4-Cl-Ph	C ₁₉ H ₁₅ ClO ₄ S
288122	3,4-(Cl)2-Ph	C ₁₉ H ₁₄ Cl ₂ O ₄ S
288123	4-Cl-PhO	C ₁₉ H ₁₅ ClO ₅ S
288124	2,4-(F)2-PhO	C ₁₉ H ₁₄ F ₂ O ₅ S

SOURCE – Almirall Prodesfarma.

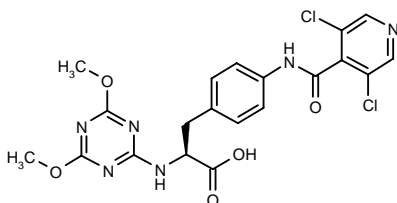
REFERENCES

1. Crespo Crespo, M.I. et al. (Almirall Prodesfarma, SA) *2-Phenylpyran-4-one derivs.* WO 0018753.

288186

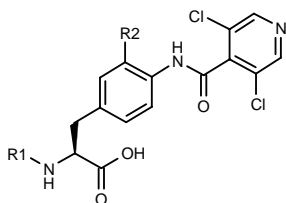
2(S)-(4,6-Dimethoxy-1,3,5-triazin-2-ylamino)-3-[4-(3,5-dichloropyridin-4-ylcarboxamido)phenyl]propionic acid

N-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-L-[4-(3,5-dichloropyridin-4-ylcarboxamido)]phenylalanine



C20 H18 Cl2 N6 O5; Mol wt: 493.3052

ACTION – Cell adhesion modulator that selectively inhibits the α_4 subgroup of integrins ($\alpha_4\beta_1$ and $\alpha_4\beta_7$), and is thus particularly useful for the treatment of immune and inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses, asthma and inflammatory bowel disease. Other specifically claimed phenylalanine derivatives include the following:



Compound	R1	R2	Formula
288188	6-[N(Et)2SO2]-4-pyrimidinyl	Cl	C ₂₃ H ₂₃ Cl ₃ N ₆ O ₅ S
288190	6-(PrNHSO2)-4-pyrimidinyl	Cl	C ₂₂ H ₂₁ Cl ₃ N ₆ O ₅ S
288195	4-MeO-6-(1-Piz)-1,3,5-triazin-2-yl	H	C ₂₃ H ₂₄ Cl ₂ N ₆ O ₄
288197	3-(PrSO2)-Ph	H	C ₂₄ H ₂₃ Cl ₂ N ₅ O ₅ S
288198	4-CF3-5-CO2H-2-pyrimidinyl	H	C ₂₁ H ₁₄ Cl ₂ F ₃ N ₅ O ₅
288199	4-[HO(CH2)3NH]-6-MeO-1,3,5-triazin-2-yl	H	C ₂₂ H ₂₃ Cl ₂ N ₇ O ₅

SOURCE – Celltech Group.

REFERENCES

1. Head, J.C. et al. (Celltech Chiroscience plc) *Phenylalanine derivs. as α_4 integrin inhibitors.* WO 0018759.

288325

Anti-human MT5-MMP monoclonal antibody

ACTION – Antibody against the transmembrane matrix metalloproteinase polypeptide MT5-MMP with potential in the treatment, prevention and diagnosis of a broad range of disorders including rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, stroke and Alzheimer's disease.

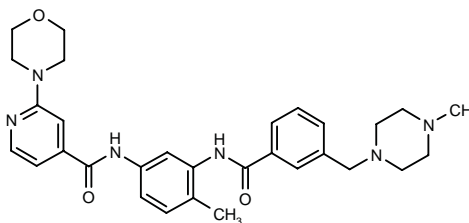
SOURCE – Kyowa Hakko.

REFERENCES

1. Hanai, N. and Furuya, A. (Kyowa Hakko Kogyo Co., Ltd.) *Novel antibodies, drugs containing these antibodies and methods for screening cpds. by using these antibodies.* WO 0018805.

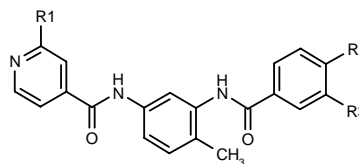
288413

N-[4-Methyl-3-[3-(4-methylpiperazin-1-ylmethyl)benz-amido]phenyl]-2-(4-morpholinyl)pyridine-4-carboxamide

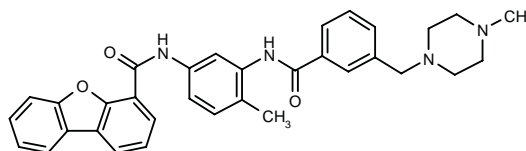


C30 H36 N6 O3; Mol wt: 528.6534

ACTION – Inhibitor of the production of cytokines, particularly TNF- α and IL-1, that acts by inhibiting p38 kinase (IC₅₀ of about 0.1 μ M against p38 α isoform). The compound inhibited lipopolysaccharide-stimulated TNF- α production in human peripheral blood mononuclear cells and in human whole blood (IC₅₀ < 0.5 and 7 μ M, respectively). It is expected to be useful in the treatment of rheumatoid arthritis and other cytokine-mediated disorders such as asthma, irritable bowel syndrome, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischemic heart disease, psoriasis, etc. Other specifically claimed benzamide derivatives include the following:



Compound	R1	R2	R3	Formula
288414	1-pyrrolidinyl	H	4-Me-1-Piz-CH2	C ₃₀ H ₃₆ N ₆ O ₂
288415	4-morpholinyl	H	4-Me-perhydro-1,4-azepin-1-yl-CH2	C ₃₁ H ₃₈ N ₆ O ₃
288416	4-morpholinyl	4-morpholinyl-(CH2)3NHCH2	H	C ₃₂ H ₄₀ N ₆ O ₄
288417	3-Me-1-Pip	H	4-Me-1-Piz-CH2	C ₃₂ H ₄₀ N ₆ O ₂
288418	4-morpholinyl	H	4-Pip-O	C ₂₉ H ₃₃ N ₅ O ₄



288419: C33 H32 N4 O3

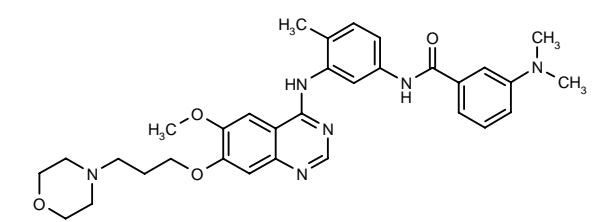
SOURCE – AstraZeneca.

REFERENCES

1. Brown, D.S. and Brown, G.R. (Zeneca, Ltd.) *Benzamide derivs. and their use as cytokine inhibitors.* WO 0018738.

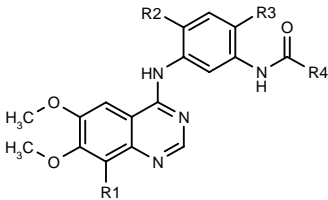
288431

3-(Dimethylamino)-N-[3-[6-methoxy-7-[3-(morpholin-4-yl)propoxy]quinazolin-4-ylamino]-4-methylphenyl]-benzamide



C32 H38 N6 O4; Mol wt: 570.6902

ACTION – Inhibitor of the production of cytokines, particularly TNF-α and IL-1, with an IC₅₀ value of about 0.1 μM against p38α kinase; it inhibited lipopolysaccharide-stimulated TNF-α production in human peripheral blood mononuclear cells with an IC₅₀ of 2 μM. It is expected to be useful in the treatment of rheumatoid arthritis and other cytokine-mediated disorders such as asthma, irritable bowel syndrome, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischemic heart disease, psoriasis, etc. Other specifically claimed benzamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
288432	H	H	Me	Ph	C ₂₄ H ₂₂ N ₄ O ₃
288433	H	H	F	Et	C ₁₉ H ₁₉ FN ₄ O ₃
288434	OMe	Me	H	3-N(Me)2-Ph	C ₂₇ H ₂₉ N ₅ O ₄

SOURCE – AstraZeneca.

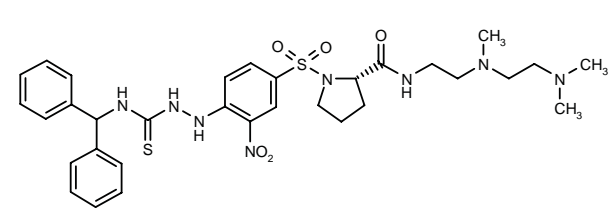
REFERENCES

1. Cumming, J.G. (Zeneca, Ltd.) *Chemical cpds.* WO 0020402.

BRADYZIDE

285606

N-[2-[N-[2-(Dimethylamino)ethyl]-N-methylamino]ethyl]-1-[4-[4-(diphenylmethyl)thiosemicarbazido]-3-nitrophenyl-sulfonyl]pyrrolidine-2(S)-carboxamide



C32 H42 N8 O5 S2; Mol wt: 682.8668

ACTION – Orally active, nonpeptide bradykinin B₂ receptor antagonist exhibiting high affinity for rodent B₂ receptors (K_i = 0.51 and 0.89 nM for inhibition of [³H]-bradykinin binding in NG108-15 cells and COS-7 cells expressing rat B₂ receptors, respectively) and much less potency at human B₂ receptors (K_i = 393 and 772 nM for inhibition of [³H]-bradykinin binding in human fibroblasts and in COS-7 cells expressing human B₂ receptors, respectively). Compound did not interact with a range of other receptors, including human B₁ receptors. Bradyzide exhibited functional competitive antagonism in NG108-15 cells where it inhibited B₂ receptor-induced ⁴⁵Ca²⁺ efflux with a pK_B of 8.0; in addition, it inhibited bradykinin-induced ventral root depolarization in the rat spinal cord and tail preparation (IC₅₀ = 1.6 nM) and bradykinin-induced contractions of isolated rat uterus (pA₂ = 8.6). *In vivo*, it exhibited long-lasting (> 4 h) oral activity in rodent models of inflammatory hyperalgesia, reversing mechanical hyperalgesia in rat knee joint induced by Freund’s complete adjuvant (ED₅₀ = 0.84 μmol/kg p.o., 0.9 μmol/kg i.v.); in this model, compound was equipotent to morphine and diclofenac and 1,000-fold more potent than paracetamol. Potentially useful as an antiinflamma-tory and analgesic agent for the treatment of chronic inflammatory diseases such as rheumatoid arthritis.

SOURCE – Novartis.

REFERENCES

1. Burgess, G.M. et al. *Bradyzide, a potent non-peptide B₂ bradykinin receptor antagonist with long-lasting oral activity in animal models of inflammatory hyperalgesia.* Br J Pharmacol 2000, 129(1): 77.

2. Dziadulewicz, E.K. et al. *1-(2-Nitrophenyl)thiosemicarbazides: A novel class of potent, orally active non-peptide antagonist for the bradykinin B₂ receptor.* J Med Chem 2000, 43(5): 769.

ISIS-24501

287824

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5’-AGATCCCGBAAGGTTCTCT-3’

ACTION – Antisense phosphorothioate oligodeoxynucleotide for modulating the expression of FAN, or factor associated with N-SMase (neutral sphingomyelinase, sphingomyelin phosphodiesterase) activation, a regulatory protein identified as a mediator of TNF-induced activation of N-SMase and considered to play a role in the inflammatory process. Compound inhibited FAN mRNA levels in human cells by 78% at 150 nM. Other exemplified antisense oligonucleotides include the following:

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5’-TCAAGGCAGGATGCTCTG-3’

ISIS-24490 [287825]

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5’-TGTGTCCGTGATGCACAC-3’

ISIS-24493 [287827]

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5’-GAGTGTATCTGGACCAC-3’

ISIS-24494 [287828]

**18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5'-TGTCAGTAGTCTCTCCAG-3'**

ISIS-24502 [287829]

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Baker, B.F. and Cowsett, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of FAN expression*. WO 0017220.

chi220

288138

Chimerized anti-human CD40 monoclonal antibody

ACTION – Chimeric anti-human CD40 monoclonal antibody that blocks the interaction between gp39 and CD40. Like the parent murine MAb (7E1), chi220 binds to CD40 and effectively blocks humoral immune responses to T-cell-dependent antigens. Potentially useful for the treatment of autoimmune diseases, inflammatory disorders and transplantation, as well as cancer. The immunosuppressive activity of the chimeric antibody was demonstrated in monkeys, and its murine counterpart displayed potent antiarthritic activity in the collagen-induced arthritis model in mice.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Aruffo, A.A. et al. (Bristol-Myers Squibb Co.) *Antibodies against human CD40*. US 6051228.

**TREATMENT OF OTHER
AUTOIMMUNE DISORDERS**

CEVIMELINE HYDROCHLORIDE

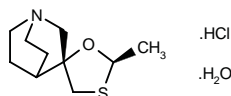
Prop INNM; USAN

134916

(±)-*cis*-2-Methylspiro[1,3-oxathiolane-5,3'-quinuclidine] hydrochloride hemihydrate

(±)-*cis*-2'-Methylspiro[1-azabicyclo[2.2.2]octane-3,5'-[1,3]oxathiolane] hydrochloride hemihydrate

AF-102B*
FKS-508
SND-5008
SNI-2011
SNK-508



C10 H17 N O S . HCl . H2O; Mol wt: 253.7920

ACTION – Muscarinic acetylcholine M₁ and M₃ receptor agonist.

INDICATION – Treatment of dry mouth (xerostomia) in patients with Sjögren's syndrome.

PRESENTATION – Capsules containing the equivalent of 30 mg cevimeline.

PROPRIETARY NAME – Evoxac (US).

SOURCES – Snow Brand; marketed by Daiichi Pharmaceutical.

SELECTED REFERENCES

1. Abe, N. and Takeshita, Y. (Snow Brand Milk Products Co., Ltd.) *Spirooxathiolane-quinuclidine deriv., for treating Sjogren syndrome*. EP 0578511, US 5340821.
2. Fisher, A. and Karton, I. (Israel Institute for Biological Research) *Novel oxathiolanes and derivs. thereof, pharmaceutical compsns. containing them and the use thereof as medicaments*. AU 8823671, EP 0314444, JP 1990062883, US 4876260.
3. Handa, H. and Takeshita, Y. (Snow Brand Milk Products Co., Ltd.) *Spirooxathiolane-quinuclidine deriv. for the treatment of xerostomia*. CA 2152420, EP 0689836, JP 1996012575, US 5580880.
4. Fox, R.I. et al. *Randomized, placebo-controlled trial of SNI-2011, a novel M3 muscarinic receptor agonist, for treatment of Sjögren's syndrome*. 62nd Annu Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 288.
5. Iga, Y. et al. *(±)-cis-2-Methylspiro [1,3-oxathiolane-5,3'-quinuclidine] hydrochloride, hemihydrate (SNI-2011, cevimeline hydrochloride) induces saliva and tear secretions in rats and mice: The role of muscarinic acetylcholine receptors*. Jpn J Pharmacol 1998, 78(3): 373.
6. Iwabuchi, Y. and Masuhara, T. *Sialogogic activities of SNI-2011 compared with those of pilocarpine and McN-A-343 in rat salivary glands: Identification of a potential therapeutic agent for treatment of Sjögren's syndrome*. Gen Pharmacol 1994, 25(1): 123.
7. Iwabuchi, Y. et al. *Salivary secretion and histopathological effects after single administration of the muscarinic agonist SNI-2011 in MRL/lpr mice*. Arch Int Pharmacodyn Ther 1994, 328(3): 315.
8. Masunaga, H. et al. *Long-lasting salivation induced by a novel muscarinic receptor agonist SNI-2011 in rats and dogs*. Eur J Pharmacol 1997, 339(1): 1.
9. Ninomiya, T. et al. *The pharmacological profile of cevimeline (SNI-2011) - A novel muscarinic agonist for the treatment of xerostomia in various models*. 62nd Annu Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 1777.
10. Ohtani, Y. et al. *Phase I study of FKS-508 - Single and multiple dose studies*. Eur J Pharmacol 1990, 183(3): Abst P.tu.412.
11. Sakai, I. et al. *Effects of long-term SNI-2011 administration on xerostomia in Sjögren syndrome*. Ryumachi 1999, 39(2): Abst W 7-4.
12. Skowronski, M.T. et al. *Mechanisms underlying SNI-2011-induced amylase secretion from rat parotid glands*. Jpn J Pharmacol 2000, 82(Suppl. 1): Abst P-405.
13. *Daiichi Pharmaceutical will market cevimeline in the U.S.* DailyDrugNews.com (Daily Essentials) 1999, June 1.
14. *New hope for patients suffering from Sjogren's syndrome: FDA approves cevimeline*. DailyDrugNews.com (Daily Essentials) 2000, April 26.
15. *Nippon Kayaku: Annual Report 1998*. DailyDrugNews.com (Daily Essentials) 1999, Jan 25.
16. *Snow Brand reports new developments concerning cevimeline*. DailyDrugNews.com (Daily Essentials) 1999, Jan 22.

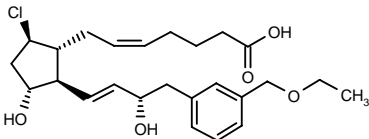
MONOGRAPH – Sorbera, L. and Castañer, J. *Cevimeline hydrochloride*. Drugs Fut 2000, 025(06): 0558.

*See **AF-102B** published with incorrect structure Drug Data Rep 1988, 010(04): 0273.

IMMUNOMODULATING AGENTS

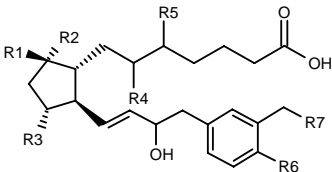
287634

9-Chloro-9-deoxy-16-[3-(ethoxymethyl)phenyl]-17,18,19,20-tetranorprostaglandin F_{2β}

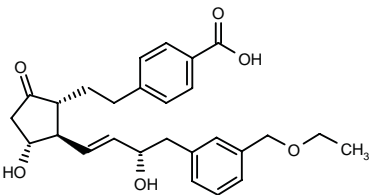


C25 H35 Cl O5; Mol wt: 450.9995

ACTION – Agent with high binding affinity for PGE₂ receptors, especially the EP₄ subtype, with potential in the treatment of autoimmune diseases such as amyotrophic lateral sclerosis (ALS), organ transplant rejection, asthma, bone dysplasia, neurodegeneration, lung and liver failure, as well as sleep and platelet aggregation disorders. In binding assays, compound exhibited K_i values of 0.0015 and 0.04 μM, respectively, for murine EP₄ and EP_{3α} receptors expressed in CHO cells. Compound is reported to have low toxicity. Other compounds from this series of ω-substituted phenyl-prostaglandin E derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	Isomer	Formula
287636	-O-	OH	H	H	H	H	OMe	S	C ₂₄ H ₃₄ O ₆
287637	-O-	OH	H	H	H	H	CH ₂ F	S	C ₂₄ H ₃₃ FO ₅
287638	-O-	OH	H	H	H	OH	H	S	C ₂₃ H ₃₂ O ₆
287639	-O-	OH	(Z)-bond	H	OH	OH	Et	S	C ₂₅ H ₃₄ O ₆
287642	-O-	H	(Z)-bond	H	OH	OH	OMe	S	C ₂₄ H ₃₂ O ₅
287645	Cl	H	OH	(Z)-bond	OH	OH	OMe		C ₂₄ H ₃₃ ClO ₆
287647	F	H	OH	(Z)-bond	H	OH	OPr		C ₂₆ H ₃₇ FO ₅



287648: C27 H32 O6

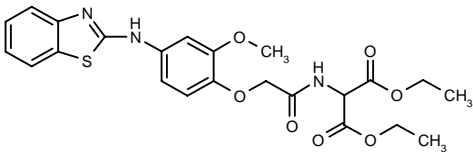
SOURCE – Ono.

REFERENCES

1. Maruyama, T. and Ohuchida, S. (Ono Pharmaceutical Co., Ltd.) ω-Substd. phenyl-prostaglandin E derivs. and drugs containing the same as the active ingredient. WO 0015608.

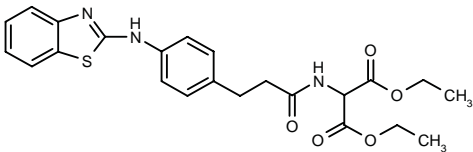
287650

2-[2-[4-(Benzothiazol-2-ylamino)-2-methoxyphenoxy]-acetamido]malonic acid diethyl ester



C23 H25 N3 O7 S; Mol wt: 487.5305

ACTION – An inhibitor of cell adhesion molecules, particularly ICAM-1 and VCAM-1, with potential as an immunosuppressant, antiinflammatory, antiallergic and antimetastatic agent. *In vitro*, compound was shown to completely inhibit the adhesion of U937 cells to IL-1β-stimulated human umbilical vein endothelial cells (HUVEC) at a concentration of 10 μM. Compound was also effective in a delayed-type hypersensitivity reaction in rats following oral administration of 30 mg/kg. Another compound from this series of malonic diester derivatives is:



287651: C23 H25 N3 O5 S

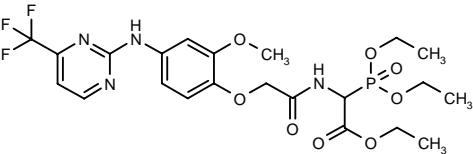
SOURCE – Kyorin.

REFERENCES

1. Kono, Y. et al. (Kyorin Pharmaceutical Co., Ltd.) Malonic diester derivs. and process for producing the same. WO 0015604.

287653

2-(Diethoxyphosphoryl)-2-[2-[2-methoxy-4-[4-(trifluoromethyl)pyrimidin-2-ylamino]phenoxy]acetamido]acetic acid ethyl ester



C22 H28 F3 N4 O8 P; Mol wt: 564.4512

ACTION – Cell adhesion molecule inhibitor with potential as an immunosuppressant, antiinflammatory, antiallergic and antimetastatic agent. *In vitro*, compound produced 88% inhibition of the adhesion of U937 cells to IL-1β-stimulated human umbilical vein endothelial cells (HUVEC) at a concentration of 10 μM. Compound was also effective in a delayed-type hypersensitivity reaction in rats following oral administration of 30 mg/kg. A representative compound from a series of phosphonic ester derivatives.

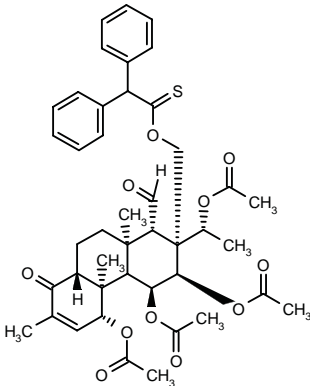
SOURCE – Kyorin.

REFERENCES

1. Kono, Y. et al. (Kyorin Pharmaceutical Co., Ltd.) *Phosphonic ester derivs. and process for producing the same.* WO 0015645.

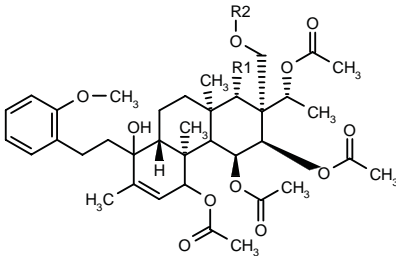
288238

(4*R*,4*aR*,5*S*,6*R*,7*R*,8*S*,8*aR*,10*aR*)-4,5,6-Tris(acetoxy)-7-[1(*R*)-(acetoxy)ethyl]-8-formyl-2,4*a*,8*a*-trimethyl-7-(2,2-diphenylthioacetoxymethyl)-1,4,4*a*,4*b*,5,6,7,8,8*a*,9,10,10*a*-dodecahydrophenanthrene-1-one

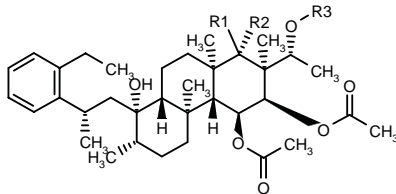


C43 H50 O11 S; Mol wt: 774.9230

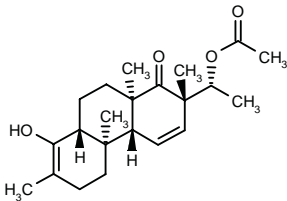
ACTION – Immunosuppressive agent that acts by inhibiting voltage-gated Kv1.3 potassium channels and is expected to be useful in the treatment of autoimmune diseases and in the prevention or therapy of transplant rejection. Other specifically claimed triterpene derivatives are:



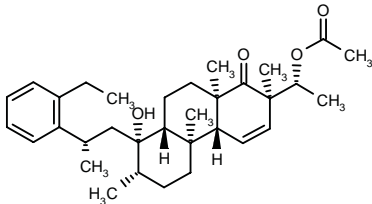
Compound	R1	R2	Isomer	Formula
288239	CHO	CSCH(Ph)2	4R	C ₅₂ H ₆₂ O ₁₂ S
288240	CH2OH	H	4R	C ₃₈ H ₅₄ O ₁₂
288241	CH2OMe	Me	4S	C ₄₀ H ₅₈ O ₁₂



Compound	R1	R2	R3	Formula
288243	H	OH	Ac	C ₃₇ H ₅₆ O ₈
288245	H	OH	H	C ₃₅ H ₅₄ O ₇
288246	H	OAc	Ac	C ₃₉ H ₅₈ O ₉
288247	H	OH	Ac	C ₃₇ H ₅₆ O ₈
288248	-O-		Ac	C ₃₇ H ₅₄ O ₈



288242: C22 H32 O4



288244: C33 H48 O4

SOURCE – Merck & Co.

REFERENCES

1. Bao, J. et al. (Merck & Co., Inc.) *Immunosuppressant tricyclic cpds.* US 6051590.

HUMAN INTERFERON EPSILON

287955

ACTION – Polypeptide from the interferon family with antiviral, immunomodulating and antiproliferative activity. Its murine homologue, as well as nucleic acids encoding these molecules, expression vectors, fusion proteins and antibodies, are also disclosed.

SOURCE – ZymoGenetics.

REFERENCES

1. Conklin, D.C. et al. (ZymoGenetics, Inc.) *Interferon-epsilon.* WO 0017361.

INTERLEUKIN-B50

287954

IL-B50

ACTION – Cytokine with significant sequence and structural similarity to IL-7, believed to exhibit stimulatory or inhibitory effects on hematopoietic cells including T-cells, B-cells, natural killer (NK) cells, macrophages, dendritic cells and hematopoietic progenitors. It is thus potentially useful for modulating or intervening in the immune response. Nucleic acids encoding this molecule, as well as expression vectors, methods for its production and specific antibodies, are also disclosed.

SOURCE – Schering-Plough.

REFERENCES

1. Bazan, J.F. (Schering Corp.) *Human interleukin-B50, therapeutic uses.* WO 0017362.

OMP21

288469

Polypeptide isolated from the outer membrane of Moraxella catarrhalis with an apparent molecular weight between 16 and 20 kDa

ACTION – Protein isolated from the outer membrane of *Moraxella catarrhalis* and also obtained by recombinant technology. Polynucleotides encoding this protein and antibodies that specifically bind OMP21 are also claimed, as well as their use in vaccines protecting against *M. catarrhalis* infections including otitis media, respiratory infections, sinusitis and pneumonia.

SOURCE – Antex Biologics.

REFERENCES

1. Tucker, K. and Tillman, U.F. (Antex Biologics Inc.) *Moraxella catarrhalis* protein, nucleic acid sequence and uses thereof. WO 0018910.

SEAM-18

287956

Monoclonal antibody against an N-propionylated Neisseria meningitidis serogroup B capsular polysaccharide

ACTION – Bactericidal antibody directed against an *N*-propionylated *Neisseria meningitidis* serogroup B (MenB) capsular polysaccharide that does not crossreact or is minimally crossreactive with host tissues. Methods of obtaining and using the same, as well as peptide mimetics identified using the novel antibodies that elicit serum antibody for use in the preparation of vaccines, are also disclosed, as are methods for the treatment and/or prevention of MenB and *Escherichia coli* K1 disease. Another specifically claimed antibody is:

Monoclonal antibody against an N-propionylated Neisseria meningitidis serogroup B capsular polysaccharide

SEAM-12 [287957]

SOURCES – Children's Hospital Medical Center, Oakland, Oakland, CA (US); Chiron.

REFERENCES

1. Granoff, D.M. and Moe, G.R. (Chiron Corp.;Children's Hospital Medical Center of Northern California) *Antibodies that define unique meningococcal B epitopes and vaccine compsns.*. US 6048527.

TANGO-191

288308

ACTION – Secreted immunomodulatory protein, a transmembrane protein expressed in the spleen, lymph node, peripheral blood lymphocytes and bone marrow that appears to be a member of the IL-1 superfamily with some similarity to the IL-1 receptor. TANGO-191 polypeptides and modulators are useful in the treatment of immune, autoimmune and inflammatory disorders.

SOURCE – Millennium BioTherapeutics.

REFERENCES

1. Busfield, S.J. (Millennium BioTherapeutics, Inc.) *Novel secreted immunomodulatory proteins and uses thereof.* WO 0018800.

TANGO-195

288309

ACTION – Secreted immunomodulatory protein, a type I transmembrane protein belonging to the CD2 subgroup of the immunoglobulin superfamily. It is expressed in the spleen, thymus, lymph node and bone marrow, as well as in activated human monocytes/macrophages and, at lower levels, in activated human lymphocytes. This protein has been suggested to regulate cytokine-induced differentiation of T-cells and to play a role in B-cell leukemia, the immune response and autoimmune disorders.

SOURCE – Millennium BioTherapeutics.

REFERENCES

1. Busfield, S.J. (Millennium BioTherapeutics, Inc.) *Novel secreted immunomodulatory proteins and uses thereof.* WO 0018800.

ONCOLYTIC DRUGS

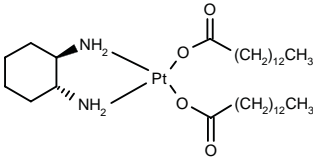
DNA-DAMAGING DRUGS

SM-11355*

126391

(*SP*-4-2)-[(1*R*,2*R*)-1,2-Cyclohexanediamine-κ*N*,κ*N*']-bis(myristato-κ*O*)platinum(II)

DACHPM
DACHPt(II)(Myr)₂



C28 H54 O4 Pt . C6 H14 N2; Mol wt: 764.0012

OMP21

288469

Polypeptide isolated from the outer membrane of Moraxella catarrhalis with an apparent molecular weight between 16 and 20 kDa

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SOURCE – Antex Biologics.

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SEAM-18

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288308

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1. Busfield, S.J. (Millennium BioTherapeutics, Inc.) *Novel secreted immunomodulatory proteins and uses thereof.* WO 0018800.

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SOURCE – Millennium BioTherapeutics.

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1. Busfield, S.J. (Millennium BioTherapeutics, Inc.) *Novel secreted immunomodulatory proteins and uses thereof.* WO 0018800.

ONCOLYTIC DRUGS

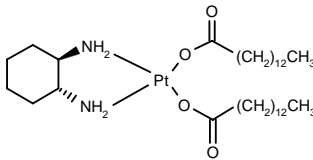
DNA-DAMAGING DRUGS

SM-11355*

126391

(*SP*-4-2)-[(1*R*,2*R*)-1,2-Cyclohexanediamine-κ*N*,κ*N*']-bis(myristato-κ*O*)platinum(II)

DACHPM
DACHPt(II)(Myr)₂



C28 H54 O4 Pt . C6 H14 N2; Mol wt: 764.0012

ACTION – Antineoplastic agent, a lipophilic platinum complex with good cytotoxic activity, when suspended in Lipiodol to form a stable colloidal suspension, against various human tumor cell lines including hepatoblastoma HepG2, renal carcinoma KU-2, lung carcinoma QG-56 and PC-8, and colon carcinoma WiDr cells ($IC_{50} = 1.3, 0.61, 3, 4.6$ and $3.7 \mu M$, respectively) following 7-day exposure. In an intrahepatic arterial chemotherapy model in rats, compound (0.2 and 0.4 mg) suspended in Lipiodol exhibited higher antitumor activity than the complex cisplatin/Lipiodol, producing almost complete disappearance of tumors after 4 weeks of treatment at doses that showed no hepatic toxicity. Preliminary results from a phase II clinical trial in patients with hepatocellular carcinoma demonstrated that compound given intraarterially as a Lipiodol emulsion at doses of 20-120 mg has significant antitumor activity and is well tolerated.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Maeda, M. and Sasaki, T. (Sumitomo Pharmaceuticals Co., Ltd.) *Liposoluble platinum (II) complex and preparation thereof*. AU 8654358, EP 0193936, JP 1987000096.
2. Kishimoto, S. et al. *Antitumor effects of a novel lipophilic platinum complex (SM-11355) against a slowly-growing rat hepatic tumor after intra-hepatic arterial administration*. Biol Pharm Bull 2000, 23(3): 344.
3. Kishimoto, S. et al. *In vitro antitumor activity, intracellular accumulation, and DNA adduct formation of cis[[(1R, 2R)-1,2-cyclohexanediamine-N,N']bis (myristato)] platinum (II) suspended in Lipiodol*. Jpn J Cancer Res 2000, 91(1): 99.
4. Kishimoto, S. et al. *In vitro cytotoxicity of cis[[(1R,2R)-1,2-cyclohexanediamine-N,N']bis(myristato)] platinum(II) suspended in Lipiodol in rat hepatoma AH-109A cells and human tumor cell lines*. Biol Pharm Bull 2000, 23(4): 487.
5. Kishimoto, S. et al. *In vitro release of SM-11355, cis[[(1R,2R)-1,2-cyclohexanediamine-N,N']bis(myristato)] platinum (II) suspended in Lipiodol*. Biol Pharm Bull 2000, 23(5): 637.
6. Kitamoto, M. et al. *Phase II trial of a novel intra-arterial lipophilic platinum derivative (SM-11355) in patients with hepatocellular carcinoma (HCC)*. Proc Am Soc Clin Oncol 2000, 19: Abst 1163.
7. Miyazawa, K. et al. *In vitro antitumor activity, intracellular accumulation, and DNA adduct formation of cis[[(1R, 2R)-1,2-cyclohexanediamine-N,N']bis (myristato)] platinum (II) suspended in Lipiodol*. Drug Deliv Syst 1999, 14(5): 401.
8. Ono, Y. et al. *The effect of liposoluble cis platinum-II complex administered via hepatic artery on rat hepatic carcinoma*. J Jpn Soc Cancer Ther 1992, 27(1): 49.
9. *SM-11355 development status*. Sumitomo Pharmaceuticals Co., Ltd. Company Communication 2000, Jan 12.

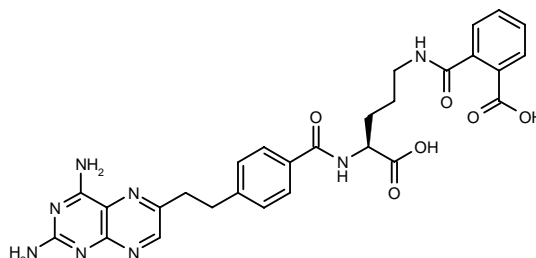
Identified compound **DACHPI(II(Myristato))₂** Drug Data Rep 1987, 009(03): 0269.

ANTIMETABOLITES

287239

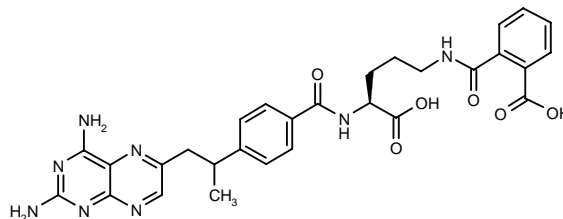
*N*²-[4-[2-(2,4-Diaminopteridin-6-yl)ethyl]benzoyl-*N*⁵-hemiphthaloyl-L-ornithine

2-[*N*-[4(*S*)-Carboxy-4-[4-[2-(2,4-diaminopteridin-6-yl)ethyl]benzamido]butyl]carbamoyl]benzoic acid



C₂₈ H₂₈ N₈ O₆; Mol wt: 572.5792

ACTION – Antineoplastic agent, an analogue of the antifolate PT-523 with potent cytotoxic activity against human leukemia CCRF-CEM cells ($IC_{50} = 0.53 \text{ nM}$). Another representative compound within this series of nonpolyglutamatable antifolates is:



288081: C₂₉ H₃₀ N₈ O₆

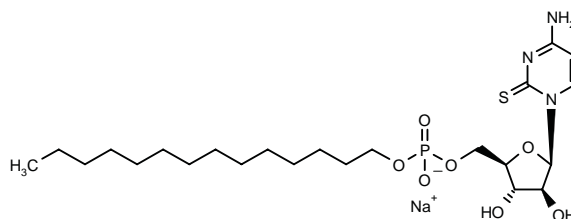
SOURCES – Dana-Farber Cancer Institute, Boston, MA (US); Harvard Medical School, Boston, MA (US).

REFERENCES

1. Rosowsky, A. et al. *Analogues of the potent nonpolyglutamatable antifolate *N*⁶-(4-amino-4-deoxypteroyl)-*N*⁸-hemiphthaloyl-L-ornithine (PT523) with modifications in the side chain, *p*-aminobenzoyl moiety, or 9,10-bridge: Synthesis and in vitro antitumor activity*. J Med Chem 2000, 43(8): 1620.
2. Rosowsky, A. et al. *Efficient transport and in vitro cytotoxicity of 10-deaza and other analogs of *N*⁶-(4-amino-4-deoxypteroyl)-*N*⁸-hemiphthaloyl-L-ornithine (PT523)*. Proc Amer Assoc Cancer Res 2000, 41: Abst 24.

288131

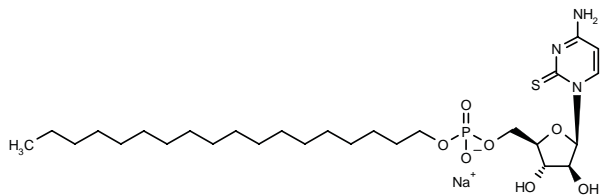
1-[5'-*O*-[Hydroxy(tetradecyloxy)phosphoryl]-β-D-arabinofuranosyl]-2-thiocytosine sodium salt



C₂₃ H₄₁ N₃ Na O₇ P S; Mol wt: 557.6209

M.p. 200 °C (decomp.).

ACTION – Antineoplastic agent, a derivative of araSC with antitumor activity in mice bearing leukemia P388 leukemia, as shown by its ability to prolong survival time at doses of 75-300 mg/kg i.p. (approximately 200% increase in survival at 300 mg/kg), without inducing substantial body weight loss. Compound appears to act as a prodrug regenerating the parent compound araSC following enzymatic and/or chemical hydrolysis in the body, and showed low reactivity with plasma and liver enzymes, indicating potentially prolonged release of araSC. Another araSC derivative is:



288132: C27 H49 N3 Na O7 P S

SOURCE – Toagosei.

REFERENCES

1. Saneyoshi, M. et al. (Toagosei Co., Ltd.) 2-Thiocytosinearabinoside-5'-phosphoric acid alkyl ester, its preparation method, and anti-cancer agent containing it as active ingredient. JP 1998087688.

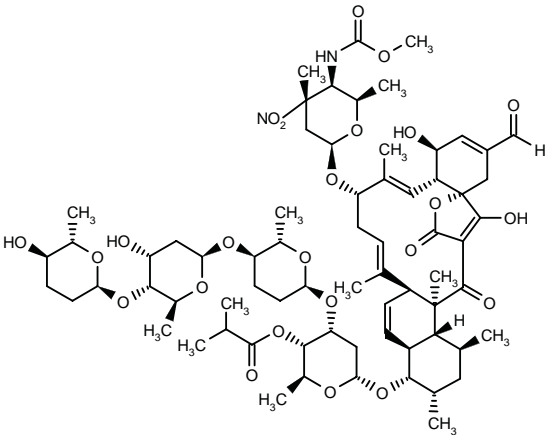
2. Kawaguchi, T. et al. Enzymatic reactivity and anti-tumor activity of 1-(β-D-arabinofuranosyl)-2-thiocytosine derivatives. Chem Pharm Bull 2000, 48(4): 454.

ANTIBIOTICS AND ALKALOIDS

ARISOSTATIN A

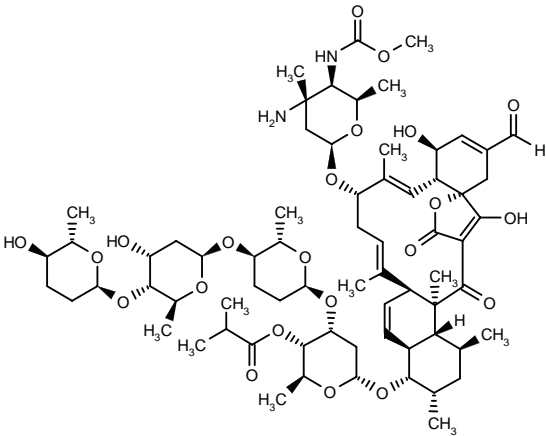
287122

(1*S*,5*S*,6*R*,9*S*,13*S*,16*S*,17*S*,18*S*,20*S*,21*R*,22*S*)-5,27-Dihydroxy-17-[2,3,6-trideoxy-α-L-glucopyranosyl-(1→4)-2,6-dideoxy-β-L-allopyranosyl-(1→4)-2,3,6-trideoxy-α-L-glucopyranosyl-(1→3)-2,6-dideoxy-4-*O*-(2-methylpropionyl)-α-L-allopyranosyloxy]-9-[5(*R*)-(methoxycarbonylamino)-4(*S*),6(*R*)-dimethyl-4-nitrotetrahydropyran-2-yloxy]-8,12,18,20,22-pentamethyl-23,25-dioxo-26-oxapentacyclo[22.2.1.0^{1,6}.0^{13,22}.0^{16,21}]heptacos-3,7,11,14,24(27)-pentaene-3-carbaldehyde



C69 H100 N2 O24; Mol wt: 1341.5390

ACTION – Antibiotic extracted from the fermentation broth of *Micromonospora* sp. TP-A0316, with antibacterial activity against Gram-positive bacteria including *Bacillus subtilis* ATCC 6633, *Micrococcus luteus* ATCC 9431 and *Staphylococcus aureus* 209P JC-1 (MIC = 0.39, 12.5 and 100 µg/ml, respectively), but inactive against Gram-negative bacteria and yeasts. Compound also showed cytotoxic activity *in vitro* against human myeloid leukemia U937 cells (IC₅₀ = 0.4 µg/ml) and against cancer cell lines derived from breast, brain, lung and colon (IC₅₀ = 0.059-0.26 µM). The compound was shown to inhibit neuritogenesis in nerve growth factor (NGF)-stimulated PC12 cells at concentrations below 1 µM via inhibition of tubulin polymerization. Another member of this class of tetrocarcin antibiotics is:



Arisostatin B [287123]: C69 H102 N2 O22

SOURCES – Tamagawa University, Tokyo (JP); Toyama Prefectural University, Toyama (JP).

REFERENCES

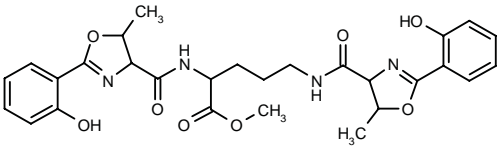
1. Furumai, T. et al. Arisostatins A and B, new members of tetrocarcin class of antibiotics from *Micromonospora* sp. TP-A0316. I. Taxonomy, fermentation, isolation and biological properties. J Antibiot 2000, 53(3): 227.

2. Igarashi, Y. et al. Arisostatins A and B, new members of tetrocarcin class of antibiotics from *Micromonospora* sp. TP-A0316. II. Structure determination. J Antibiot 2000, 53(3): 233.

BE-70016

287379

2,5-Bis[2-(2-hydroxyphenyl)-5-methyl-4,5-dihydrooxazol-4-ylcarboxamido]pentanoic acid methyl ester



C28 H32 N4 O8; Mol wt: 552.5808

ACTION – Antineoplastic agent isolated from *Actinoplanes* sp. A70016 (FERM P-16791), found to inhibit the growth of murine leukemia P388 and human lung cancer PC-13 cells with respective IC₅₀ values of 0.97 and 1.38 µg/ml.

SOURCE – Banyu.

REFERENCES

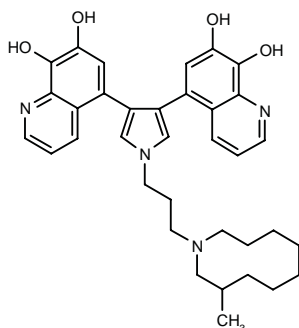
1. Shimokawa, H. et al. (Banyu Pharmaceutical Co., Ltd.) *Anti-tumor substance BE-70016 and its preparation method*. JP 2000053660.

HALITULIN

288427

3,4-Bis(7,8-dihydroxyquinolin-5-yl)-1-[3-(3-methylperhydroazecin-1-yl)propyl]-1*H*-pyrrole

5,5'-[1-[3-(3-Methylperhydroazecin-1-yl)propyl]-1*H*-pyrrol-3,4-ylidene]bis(quinoline-7,8-diol)



C35 H40 N4 O4; Mol wt: 580.7250

ACTION – Antitumor alkaloid isolated from the Indo-Pacific sponge *Haliclona tulearensis*. It was found to have cytotoxic activity against murine leukemia P388, human lung carcinoma A549, human colon carcinoma HT-19 and human melanoma MEL-28 cells with IC₅₀ values of 0.025, 0.0125, 0.0125 and 0.025 µg/ml, respectively.

SOURCE – Pharma Mar.

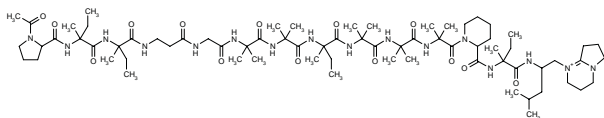
REFERENCES

1. Kashman, Y. et al. (Pharma Mar, SA) *Cytotoxic alkaloids (halitulin)*. WO 0020411.

PF-1201

288572

1-[2-[*N*-Acetyl-DL-prolyl-DL-(α-ethyl)alanyl-DL-(α-ethyl)alanyl-β-alanyl-glycyl-(2-aminoisobutyryl)-(2-aminoisobutyryl)-DL-(α-ethyl)alanyl-(2-aminoisobutyryl)-(2-aminoisobutyryl)-(2-aminoisobutyryl)-(piperidin-2-ylcarbonyl)-DL-(α-ethyl)alaninamido]-4-methylpentyl]-2,3,4,6,7,8-hexahydropyrrolo[1,2-*a*]pyrimidin-1-ium



C71 H123 N16 O14; Mol wt: 1424.8510

ACTION – Antitumor antibiotic isolated from *Chyso-sporium* PF1201 (FERM P-16717) and shown to have selective antiproliferative activity against tumor gene-transformed cells, as demonstrated *in vitro* by IC₅₀ values of 6.4-49 ng/ml against adenovirus tumor gene-transformed rat glial cells and fibroblasts compared to values of 13,000-16,000 ng/ml obtained against normal rat glial cells and fibroblasts.

SOURCE – Meiji Seika.

REFERENCES

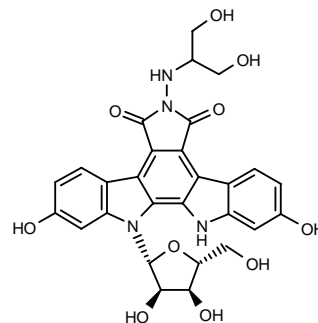
1. Yaguchi, T. et al. (Meiji Seika Kaisha, Ltd.) *Novel antitumor antibiotic PF1201, its preparation method, and antitumor agent containing it as active ingredient*. JP 2000072798.

DNA-INTERCALATING DRUGS

J-109534*

250703

12-(β-D-Ribofuranosyl)-2,10-dihydroxy-6-[2-hydroxy-1-(hydroxymethyl)ethylamino]-6,7,12,13-tetrahydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione



C28 H26 N4 O10; Mol wt: 578.5400

M.p. > 250 °C; [α]_D +72.2°(c 1.00, DMSO).

ACTION – Antineoplastic agent, an analogue of the potent and selective topoisomerase I inhibitor J-107088 with improved activity against topoisomerase I in both enzyme (IC₅₀ = 8 and 51 nM, respectively) and cellular assays (EC₂₀₀ = 32 and 100 nM, respectively, in murine leukemia P388 cells); despite its higher potency against topoisomerase I, compound showed comparable or lower cytotoxic activity compared to J-107088 against P388 (IC₅₀ = 1.8 and 1.5 nM, respectively) and human stomach cancer MKN-45 cells (IC₅₀ = 50 and 4.8 nM, respectively). *In vivo*, compound was at least 6-fold less potent than the parent drug against MKN-45 xenografts in mice and showed a smaller therapeutic index.

SOURCE – Banyu.

REFERENCES

1. Kojiri, K. et al. (Banyu Pharmaceutical Co., Ltd.) *Antitumor indolopyrrolocarbazole derivs*. WO 9709339.

2. Ohkubo, M. et al. *Synthesis and biological activities of NB-506 analogues modified at the glucose group*. Bioorg Med Chem Lett 2000, 10(5): 419.

*Identified compound **250703** (see **250031**) Drug Data Rep 1997, 019(07): 0660.

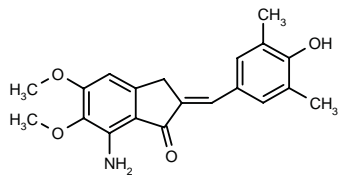
ANTIMITOTIC DRUGS

INDANOCINE

286872

7-Amino-2-[(E)-4-hydroxy-3,5-dimethylbenzylidene]-5,6-dimethoxyindan-1-one

NSC-698666



C20 H21 N O4; Mol wt: 339.3889

ACTION – Cytotoxic agent active against a number of both wild-type and multidrug-resistant human cancer cell lines including breast carcinoma MCF-7, uterine sarcoma MESS-SA, acute promyelocytic leukemia HL-60 and lymphoblastoid CEM cells (IC₅₀ = 10-85 nM and 2-25 nM against wild-type and multidrug-resistant cells, respectively). Compound was shown to block tubulin polymerization and to induce apoptotic cell death in stationary-phase multidrug-resistant cancer cells at concentrations that do not impair the viability of normal nonproliferating cells. A lead compound for the development of antineoplastic agents for the treatment of drug-resistant malignancies.

SOURCES – University of California, San Diego, La Jolla, CA (US); National Cancer Institute, Bethesda, MD (US).

REFERENCES

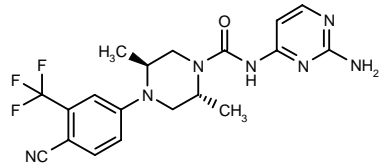
1. Leoni, L.M. et al. *Indanocine, a microtubule-binding indanone and a selective inducer of apoptosis in multidrug-resistant cancer cells.* J Natl Cancer Inst 2000, 92(3): 217.

2. Shih, H. et al. *Rational design, synthesis and structure-activity relationships of antitumor (E)-2-benzylidene-1-tetralones and (E)-2-benzylidene-1-indanones.* Bioorg Med Chem Lett 2000, 10(5): 487.

HORMONAL AGENTS

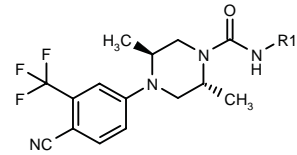
287801

N-(2-Aminopyrimidin-4-yl)-4-[4-cyano-3-(trifluoromethyl)phenyl]-2(R),5(S)-dimethylpiperazine-1-carboxamide



C19 H20 F3 N7 O; Mol wt: 419.4090

ACTION – Antiandrogenic agent with high affinity for the rat androgen receptor (K_i = 1.81 nM) and potential for the treatment or prevention of prostate cancer and prostatic hypertrophy. Within this series of cyanophenyl derivatives, the following compounds are also included:



Compound	R1	Formula
287802	2-Br-4-Pyr	C ₂₀ H ₁₉ BrF ₃ N ₅ O
287805	6-MeO-3-Pyr	C ₂₁ H ₂₂ F ₃ N ₅ O ₂
287809	2-(MeNHCO)-4-Pyr	C ₂₂ H ₂₃ F ₃ N ₆ O ₂
287810	6-CF ₃ -3-Pyr	C ₂₁ H ₁₉ F ₆ N ₅ O
287811	6-CN-3-Pyr	C ₂₁ H ₁₉ F ₃ N ₆ O
287814	2-F-4-Pyr	C ₂₀ H ₁₉ F ₄ N ₅ O

SOURCE – Yamanouchi.

REFERENCES

1. Taniguchi, N. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Cyanophenyl derivs.* WO 0017163.

CANCER IMMUNOTHERAPY

DANTON

287083

Anti-human major histocompatibility complex (MHC) class II, HLA-DR-specific monoclonal antibody

ACTION – Anti-human major histocompatibility complex (MHC) class II monoclonal antibody that specifically binds to HLA-DR-expressing tumor cells and triggers apoptosis in such cells. An important feature of the anti-class II MHC MAbs is their lack of simultaneous suppression of class II-dependent immune responses. This MAb was shown to induce over 75% cell death in two human B-cell tumor lines while having no effect in normal human lymphocytes, and it was also found to significantly prolong survival in SCID mice bearing HLA-DR+ human plasmacytoma MC/CAR tumors.

SOURCE – Dendreon.

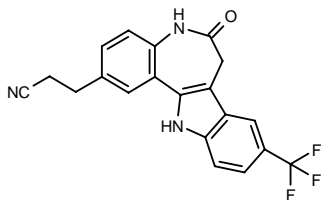
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1. Vidovic, D. and Laus, R. (Dendreon Corp.) *Selective apoptosis of neoplastic cells by an HLA-DR specific monoclonal antibody.* WO 0012560.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

288628

3-[6-Oxo-9-(trifluoromethyl)-5,6,7,12-tetrahydroindolo-[3,2-d][1]benzazepin-2-yl]propanenitrile



C20 H14 F3 N3 O; Mol wt: 369.3446

M.p. 286° (decomp.).

ACTION – Antineoplastic agent, a cyclin-dependent kinase cdk1/cyclin B inhibitor (IC_{50} = 47 nM) with *in vitro* cytotoxic activity against a panel of 60 human tumor cell lines including human colon cancer HCT 116.

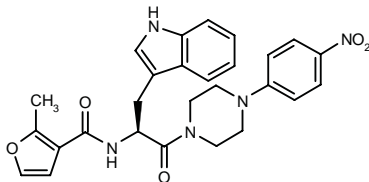
SOURCES – CNRS; Universität Hamburg, Hamburg (DE); National Cancer Institute, Bethesda, MD (US).

REFERENCES

1. Zaharevitz, D.W. et al. (Department of Health & Human Services) *Fused azepinone cyclin dependent kinase inhibitors*. WO 9965910.
2. Kunick, C. et al. *2-Substituted paullones: CDK1/cyclin B-inhibiting property and in vitro antiproliferative activity*. Bioorg Med Chem Lett 2000, 10(6): 567.

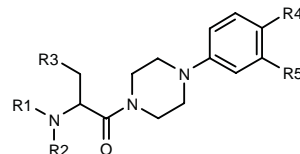
287577

1-[*N*-(2-Methylfuran-3-ylcarbonyl)-*L*-tryptophyl]-4-(4-nitrophenyl)piperazine

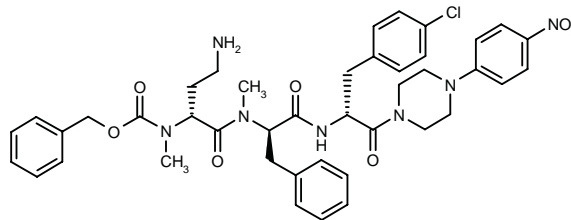


C27 H27 N5 O5; Mol wt: 501.5403

ACTION – Small-molecule compound that inhibits the interaction between the cellular proto-oncogene MDM2 and the tumor suppressor protein p53 (IC_{50} of about 4 μ M in a modified ELISA test measuring inhibition of p53/MDM2 interaction), expected to be useful in the treatment of cancers mediated by wild-type or altered MDM2. Other exemplified piperazine-4-phenyl derivatives are:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
287579	H	H	cyclohexyl	NO2	H	L	C ₁₉ H ₂₈ N ₄ O ₃
287580	cyclohexyl-CO-D-Lys-D-(N-Me)-Phe-	H	cyclohexyl	NO2	H	L	C ₄₂ H ₆₁ N ₇ O ₆
287581	cyclohexyl-CO-D-Lys-D-(N-Me)-Phe-	H	4-Cl-Ph	Cl	Cl	D	C ₄₂ H ₅₃ Cl ₃ N ₆ O ₄
287582	1-adamantyl-CH2CO-D-Lys-D-(N-Me)-Phe-	H	3-indolyl	NO2	H	D	C ₄₉ H ₆₂ N ₆ O ₆
287583	(Pr)2CHCO-D-Lys-D-(N-Me)-Phe-	H	3-indolyl	NO2	H	D	C ₄₅ H ₆₀ N ₆ O ₆
287584	2-NO2-4,5-(MeO)2-PhCO	Me	3-indolyl	NO2	H	L	C ₃₁ H ₃₂ N ₆ O ₈
287585	2-NO2-4,5-(MeO)2-PhCO	H	4-Cl-Ph	NO2	H	L	C ₂₈ H ₂₈ ClN ₆ O ₈
287587	3-thienyl-CO	H	3-indolyl	NO2	H	L	C ₂₆ H ₂₅ N ₅ O ₄ S
287588	2,6-(MeO)2-3-Pyr-CO	H	3-indolyl	NO2	H	L	C ₂₉ H ₃₀ N ₆ O ₆
287589	2,4-(Me)2-5-thiazolyl-CO	H	3-indolyl	NO2	H	L	C ₂₇ H ₂₈ N ₆ O ₄ S



287578: C42 H48 Cl N7 O7

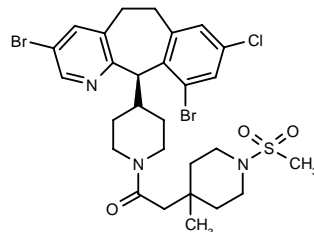
SOURCE – AstraZeneca.

REFERENCES

1. Luke, R.W.A. et al. (Zeneca, Ltd.) *Piperazine-4-phenyl derivs. as inhibitors of the interaction between MDM2 and 53*. WO 0015657.

288237

1-[4-[3,10-Dibromo-8-chloro-6,11-dihydro-5 *H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11 (*R*)-yl]piperidin-1-yl]-2-[4-methyl-1-(methylsulfonyl)piperidin-4-yl]ethan-1-one



C28 H34 Br2 Cl N3 O3 S; Mol wt: 687.9216

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras, proven to inhibit protein farnesyltransferase in an *in vitro* enzyme assay and in COS cells with respective IC_{50} values of 19 and 22 nM.

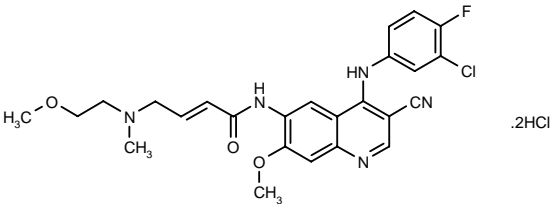
SOURCE – Schering-Plough.

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1. Taveras, A.G. (Schering Corp.) *Cpds. useful for inhibition of farnesyl protein transferase*. US 6051582.

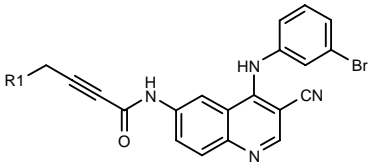
288328

N-[4-(3-Chloro-4-fluorophenylamino)-3-cyano-7-methoxyquinolin-6-yl]-4-[*N*-(2-methoxyethyl)-*N*-methylamino]-2-butenamide dihydrochloride

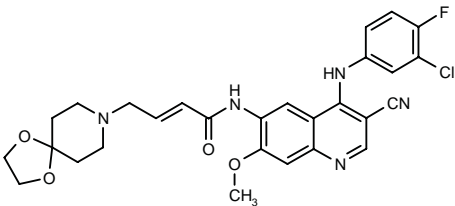


C25 H25 Cl F N5 O3 . 2HCl; Mol wt: 570.8773

ACTION – Agent for the treatment of cancer and polycystic kidney disease, an inhibitor of protein tyrosine kinases such as epidermal growth factor (EGF) receptor tyrosine kinase (IC₅₀ = 0.01 μM using recombinant enzyme). *In vitro*, compound was shown to inhibit the growth of human breast cancer MDA-MB-435, human colon cancer SW620, human epidermoid carcinoma A-431, human breast cancer SK-BR-3, 3T3 and Her2/3T3 cells with respective IC₅₀ values of 2.07, 1.53, 0.245, 0.107, 2.04 and 0.192 μg/ml. *In vivo*, compound inhibited the growth of A-431 tumors implanted s.c. into mice, giving a T/C x 100 value of 26% at day 28 after tumor implantation when administered at a dose of 10 or 40 mg/kg/day p.o. x 10 days. Other compounds from this series of substituted 3-cyanoquinolines include the following:



Compound	R1	Formula
288330	N(CH ₂ CH ₂ OMe) ₂	C ₂₆ H ₂₆ BrN ₅ O ₃
288331	N(Me)CH ₂ CH ₂ OMe	C ₂₄ H ₂₂ BrN ₅ O ₂
288332	allyl-N(Me)	C ₂₄ H ₂₀ BrN ₅ O
288333	2(S)-(MeOCH ₂)-1-pyrrolidinyl	C ₂₆ H ₂₄ BrN ₅ O ₂



288334: C28 H27 Cl F N5 O4

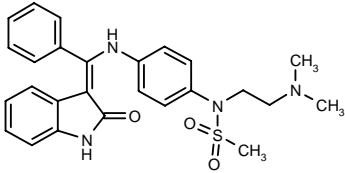
SOURCE – American Home Products.

REFERENCES

1. Wissner, A. et al. (American Cyanamid Co.) *Substd. 3-cyanoquinolines as protein tyrosine kinases inhibitors*. WO 0018740.

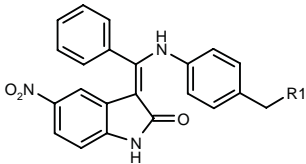
288335

(*Z*)-*N*-[2-(Dimethylamino)ethyl]-*N*-[4-[1-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)-1-(phenyl)methylamino]-phenyl]methanesulfonamide



C26 H28 N4 O3 S; Mol wt: 476.5982

ACTION – Agent with inhibitory activity against various kinases and especially cyclin-dependent kinase (CDK)/cyclin complexes. It exhibited potent antiproliferative activity *in vitro* against human uterine cancer SK-UT-1B cells (IC₅₀ = 0.15 μM). Other specifically claimed compounds from this series of substituted indolinones are:



Compound	R1	Formula
288337	N(Me) ₂	C ₂₄ H ₂₂ N ₄ O ₃
288338	4-morpholinyl-CH ₂	C ₂₇ H ₂₆ N ₄ O ₄
288339	CH ₂ N(Me) ₂	C ₂₅ H ₂₄ N ₄ O ₃
288340	1-Pip	C ₂₇ H ₂₆ N ₄ O ₃

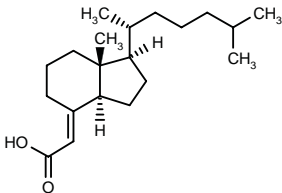
SOURCE – Boehringer Ingelheim.

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1. Walter, R. et al. (Boehringer Ingelheim Pharma KG) *Novel substd. indolinones with an inhibitory effect on various kinases and cyclin/CDK complexes*. DE 19844003, WO 0018734.

288478

2-[(1*R*,3*aR*,7*aR*)-1-[1(*R*),5-Dimethylhexyl]-7*a*-methyl-octahydro-4*H*-inden-4-ylidene]acetic acid



C20 H34 O2; Mol wt: 306.4866

ACTION – Antineoplastic agent derived from vitamin D₃, an inhibitor of the protein phosphatase cdc25A (IC₅₀ = 7.7 mcM) proven to induce cell cycle arrest of human leukemia HL60 cells in the G1 phase. Compound also exhibited cytotoxic activity against human non-small lung carcinoma SBC-5 cells (IC₅₀ = 47 μM).

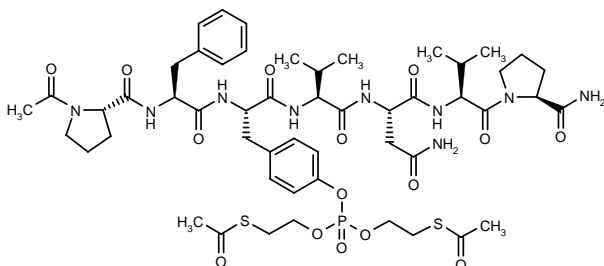
SOURCE – Taiho.

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1. Dodo, K. et al. *Synthesis of a novel class of cdc25A inhibitors from vitamin D₃*. Bioorg Med Chem Lett 2000, 10(7): 615.

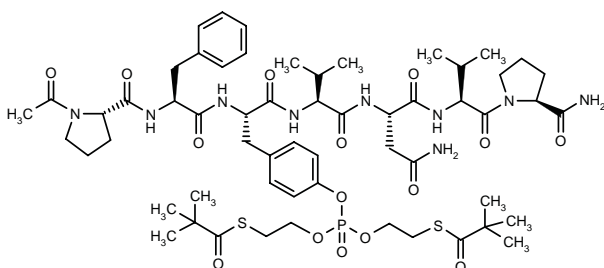
288494

N-Acetyl-L-prolyl-L-phenylalanyl-*O*-[bis[2-(acetylsulfanyl)ethoxy]phosphoryl]-L-tyrosyl-L-valyl-L-asparaginyl-L-valyl-L-prolinamide



C52 H74 N9 O15 P S2; Mol wt: 1160.3110

ACTION – Phosphopeptide prodrug that incorporates SATE (S-acyl-2-thioethyl) biolabile phosphate protection to allow penetration into cells through the bilayer cell membrane, where it delivers the monophosphate via esterase-mediated activation. Compound was able to inhibit both the Shc/Grb2 interaction and MAP kinase (ERK1 and ERK2) phosphorylation in hamster fibroblasts overexpressing human EGF (epidermal growth factor) receptors (ER22 cells). It inhibited ($IC_{50} = 1 \mu M$) colony formation in NIH3T3 cells transfected with the HER2 oncogene. Another related compound is:



288493: C58 H86 N9 O15 P S2

SOURCES – INSERM, Paris Cedex (FR); Université Montpellier II, Montpellier (FR).

REFERENCES

1. Liu, W.-Q. et al. *Inhibition of the Ras-dependent mitogenic pathway by phosphopeptide prodrugs with antiproliferative properties*. Bioorg Med Chem Lett 2000, 10(7): 669.

ISIS-24121

287978

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is:

5'-GAGGTTTATATG-GGTCAT-3', in which the central ten nucleotides are 2'-deoxynucleotides, the four nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethylnucleotides and the cytidine in position 16 is 2'-*O*-methoxyethyl-5-methylcytidine

ACTION – Antisense oligonucleotide targeted to a nucleic acid encoding human cREL, a member of the Rel/NF- κ B family of transcriptional activators, with potential in the treatment of inflammation, undesired immune responses such as graft-versus-host reaction and hyperproliferative conditions such as cancer. Compound produced 89% inhibition of cREL mRNA levels in human cells at 150 nM. Other exemplified oligonucleotides include the following:

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:

5'-ATGCCTTTTGCTTCCCAA-3'

ISIS-24089 [287979]

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is:

5'-ATGCTGCCTGCTGATCGC-3', in which the central ten nucleotides are 2'-deoxynucleotides, the four nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethylnucleotides and the cytidines in position 4, 16 and 18 are 2'-*O*-methoxyethyl-5-methylcytidines

ISIS-24117 [287980]

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is:

5'-TTTGCTTTATTGCCGTAA-3', in which the central ten nucleotides are 2'-deoxynucleotides and the four nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethylnucleotides

ISIS-24132 [287981]

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Monia, B.P. et al. (Isis Pharmaceuticals, Inc.) *Antisense modulation of cREL expression*. WO 0017400.

ISIS-25323

287982

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:

5'-CTCCCGCACTCCCTCTT-3'

ACTION – Antisense phosphorothioate oligonucleotide for modulating the expression of human RhoC, a member of the Rho subfamily of small GTPases shown to be involved in signaling pathways. *In vitro*, compound was shown to reduce human RhoC mRNA levels in human cells by 91% at 150 nM. Claimed for the treatment of hyperproliferative conditions such as cancer. Other exemplified antisense oligonucleotides include the following:

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5'-GGCACCATCCCCAACGAT-3'

ISIS-25307 [287983]

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5'-CACTTTCCTGTGAGCCAG-3'

ISIS-25340 [287984]

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is:
5'-CACTTTCCTGTGAGCCAG-3', in which the central ten nucleotides are 2'-deoxynucleotides, the four nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethynucleotides and the cytidines in positions 1, 3, 15 and 16 are 2'-*O*-methoxyethyl-5-methylcytidines

ISIS-25380 [287985]

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Cowsert, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of RhoC expression*. WO 0017224.

ISIS-25434

287986

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is:
5'-TCGGCCACATAGTTCTCG-3', in which the central ten nucleotides are 2'-deoxynucleotides, the four nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethynucleotides and the cytidines in positions 2, 15 and 17 are 2'-*O*-methoxyethyl-5-methylcytidines

ACTION – Antisense phosphorothioate oligonucleotide for modulating the expression of human RhoB, a member of the Rho subfamily of small GTPases shown to be involved in signaling pathways. *In vitro*, compound was shown to reduce human RhoB mRNA levels in human cells by 63% at 150 nM. Claimed for the treatment of hyperproliferative conditions such as cancer, as well as wound repair defects. Other exemplified antisense oligonucleotides include the following:

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is:
5'-TGTGCGGACATGCTCGTC-3', in which the central ten nucleotides are 2'-deoxynucleotides, the four nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethynucleotides and the cytidines in positions 15 and 18 are 2'-*O*-methoxyethyl-5-methylcytidines

ISIS-25442 [287987]

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is:
5'-GCCGTTCTGGGAGCCGTA-3', in which the central ten nucleotides are 2'-deoxynucleotides, the four nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethynucleotides and the cytidines in positions 2, 3 and 15 are 2'-*O*-methoxyethyl-5-methylcytidines

ISIS-25459 [287988]

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Cowsert, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of RhoB expression*. WO 0016809.

ISIS-25564

287817

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5'-CCAATCCTGTTTGCCATA-3'

ACTION – Antisense phosphorothioate oligonucleotide for modulating the expression of human RhoA, a member of the Rho subfamily of small GTPases shown to be involved in signaling pathways. *In vitro*, compound was shown to reduce human RhoA mRNA levels in human cells by 82% at 150 nM. Claimed for the treatment of hyperproliferative conditions such as cancer, as well as for the treatment of Alzheimer's disease and blood clotting disorders. Other exemplified antisense oligonucleotides include the following:

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5'-AGCTGAAGACCAGACCGT-3'

ISIS-25547 [287819]

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5'-ATACACCTCTGGGAAGT-3'

ISIS-25554 [287820]

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5'-GTGCTCATCATTCCGAAG-3'

ISIS-25561 [287822]

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5'-TAGCTCCCGCCTTGTGTG-3'

ISIS-25563 [287823]

SOURCE – Isis Pharmaceuticals.

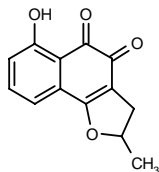
REFERENCES

1. Cowsert, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of RhoA expression*. WO 0017223.

NOCARDIONE A

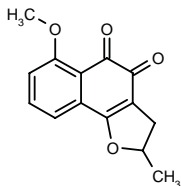
2885076-Hydroxy-2-methyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione

A-1211a



C13 H10 O4; Mol wt: 230.2180

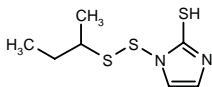
ACTION – Tyrosine phosphatase cdc25B inhibitor (IC_{50} = 17 μ M) extracted from *Nocardia* sp. TP-A0248; it also inhibited protein-tyrosine-phosphatase PTP1B and FAP-1 (IC_{50} = 14 and 89 μ M, respectively). Compound exhibited cytotoxic activity against human cervical carcinoma HeLa and human non-small cell lung carcinoma SBC-5 cells (IC_{50} = 0.38 and 0.54 μ M, respectively), and induced apoptosis-like cell death at concentrations below 6.25 μ g/ml in U937 cells. Moderate antifungal activity was also seen, with MIC values of 1.56-12.5 μ g/ml against a range of yeasts and fungi.

**Nocardione B [288508]:**C14 H12 O4
A-1211b**SOURCE** – Taiho.**REFERENCES**

1. Ohtani, T. et al. (Taiho Pharmaceutical Co., Ltd.) *A-1211 substances*. JP 2000072765.

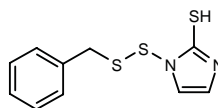
2. Otani, T. et al. *New Cdc25B tyrosine phosphatase inhibitors, nocardiones A and B, produced by Nocardia sp. TP-A0248: Taxonomy, fermentation, isolation, structural elucidation and biological properties*. J Antibiot 2000, 53(4): 337.

PX-12

2876541-(1-Methylpropyl)disulfanyl)-1*H*-imidazole-2-thiol

C7 H12 N2 S3; Mol wt: 220.3838

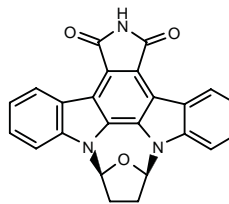
ACTION – Antineoplastic agent, a redox-regulatory agent proven to inhibit the *in vitro* activity of the redox-regulatory protein thioredoxin, stimulate apoptosis and inhibit the growth of human tumor cells in culture and of human tumor xenografts in immunodeficient mice. In asynchronous human breast cancer MCF-7 cells, compound was found to arrest the cell cycle in the G2/M phase at concentrations associated with growth-inhibitory activity. No effects were detected on the cyclin-dependent kinases cdc2 and cdc25. Pharmacokinetic studies indicated that compound has a rapid distribution or metabolism, and plasma levels declined biphasically with $t_{1/2}$ values of 2 and 48 h. Toxicity studies in mice demonstrated that compound was well tolerated after a single dose of 30 mg/kg i.p. or 25 mg/kg q.i.d. Another related compound is:

**PX-36 [287655]:** C10 H10 N2 S3**SOURCE** – ProLx.**REFERENCES**

1. Kirkpatrick, D.L. et al. *PX-12 and PX-36: Novel redox-regulatory drugs with antitumor activity: Toxicity and pharmacokinetics*. Proc Amer Assoc Cancer Res 2000, 41: Abst 4891.

2. Vogt, A. et al. *Inhibition of G2/M transition by the asymmetrical disulfide PX-12*. Proc Amer Assoc Cancer Res 2000, 41: Abst 4887.

SB-218078

288212(9*R*,12*S*)-9,12-Epoxy-2,3,9,10,11,12-hexahydro-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*k*]pyrrolo[3,4-*l*][1,6]benzodiazocine-1,3-dione

C24 H15 N3 O3; Mol wt: 393.4005

ACTION – Checkpoint kinase (chk1 kinase) inhibitor claimed for the treatment of cancer, as well as chronic inflammatory, cardiovascular and ocular proliferative disorders and benign hyperproliferative disorders such as psoriasis, rheumatoid arthritis, diabetic retinopathy and hemangiomas.

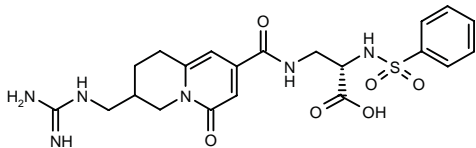
SOURCE – SmithKline Beecham.**REFERENCES**

1. Gilmarin, A.G. et al. (SmithKline Beecham Corp.) *Chk1 kinase inhibitors*. WO 0016781.

ANGIOGENESIS INHIBITORS

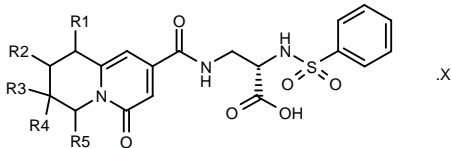
287862

3-[3-(Guanidinomethyl)-6-oxo-2,3,4,6-tetrahydro-1*H*-quinolizin-8-ylcarboxamido]-2(*S*)-(phenylsulfonamido)-propionic acid



C21 H26 N6 O6 S; Mol wt: 490.5384

ACTION – Integrin, particularly $\alpha_v\beta_3$, antagonist with IC_{50} values for fibrinogen binding to $\alpha_v\beta_3$ and gpIIb/IIIa of 0.0042 and 0.094 μ M, respectively. Compound also potently and selectively inhibited the binding of $\alpha_v\beta_3$ -transfected K562 cells to osteopontin (IC_{50} = 0.16 μ M) and the proliferation of human endothelial cells (HMVEC; IC_{50} = 1.0 μ M), and it was active in the chick chorioallantoic membrane (CAM) assay of angiogenesis. Potentially useful for inhibiting angio-genesis and/or tumor growth. Other compounds from this series of quinolizinone derivatives include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
287863	H	H	CH2NH2	H	H	CF3CO2H	C ₂₀ H ₂₄ N ₄ O ₆ S .C ₂ H ₃ F ₃ O ₂
287865	bond		O(CH2)3-NHC(=NH)NH2	bond		HCl	C ₂₃ H ₂₆ N ₆ O ₇ S .HCl
287867	bond		OCH2CH2-NHC(=NH)NH2	bond		HCl	C ₂₂ H ₂₄ N ₆ O ₇ S .HCl

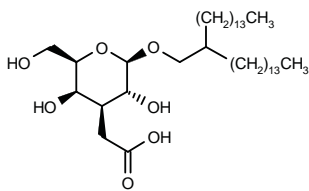
SOURCE – BioChem Pharma.

REFERENCES

1. Lamothe, S. et al. (BioChem Pharma Inc.) *Quinolizinones as integrin inhibitors*. WO 0017197.

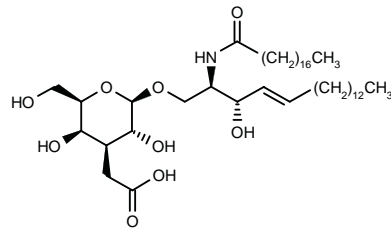
287971

3-(Carboxymethyl)-3-deoxy-1-*O*-(2-tetradecylhexadecyl)- β -D-galactopyranoside

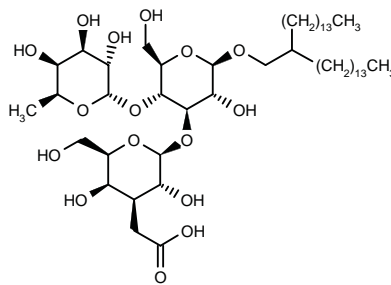


C38 H74 O7; Mol wt: 642.9956

ACTION – Selectin inhibitor with potential in the treatment of selectin-related diseases such as inflammatory disorders and cancer metastasis. *In vitro*, compound inhibited P-, L- and E-selectin binding in human promyelocytic leukemia HL-60 cells by 79 \pm 3, 92 \pm 3 and 12 \pm 8%, respectively, at a concentration of 0.3 mM. Other exemplified compounds from this series of carboxy-methylgalactose derivatives include the following:



287972: C44 H83 N O9



287973: C50 H94 O16

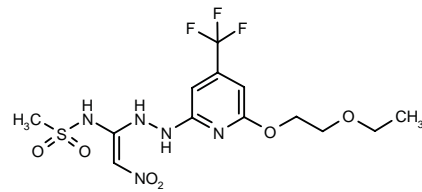
SOURCE – Otsuka.

REFERENCES

1. Kiso, M. and Ishida, H. (Otsuka Pharmaceutical Co., Ltd.) *Carboxymethylgalactose derivs*. WO 0017216.

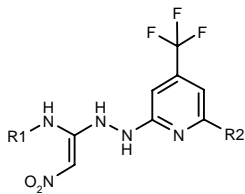
287974

N-[1-[2-[6-(2-Ethoxyethoxy)-4-(trifluoromethyl)pyridin-2-yl]hydrazino]-2-nitrovinyl]methanesulfonamide



C13 H18 F3 N5 O6 S; Mol wt: 429.3742

ACTION – Matrix metalloproteinase (MMP) inhibitor proven to inhibit human MMP-3 (stromelysin 1), MMP-7 (matrilysin) and MMP-9 (gelatinase B) activity with respective IC_{50} values of 17.8, 12.0 and 5.7 μ M. *In vivo*, compound inhibited tumor growth in mice bearing Meth A/AD fibrosarcoma by 49.8% on day 24 at a dose of 30 mg/kg/day i.p. x 11 days, and was also able to delay the development of collagen-induced arthritis in mice at a dose of 50 mg/kg/day i.p. x 5 weeks. Other compounds from this series of nitroetheneamine derivatives include the following:



Compound	R1	R2	Formula
287975	Me	Cl	C ₉ H ₉ ClF ₃ N ₅ O ₂
287976	SO ₂ Me	Cl	C ₉ H ₉ ClF ₃ N ₅ O ₄ S
287977	Me	OCH ₂ CH ₂ OEt	C ₁₃ H ₁₈ F ₃ N ₅ O ₄

SOURCE – Ishihara Sangyo.

REFERENCES

1. Kato, F. et al. (Ishihara Sangyo Kaisha, Ltd.) *Medical compsn. containing nitroetheneamine deriv. or salt thereof as active constituent.* WO 0016766.

288020

Glycosylated high-molecular-weight endostatin with a molecular weight of 22 kDa

ACTION – High-molecular-weight (HMW) endostatin useful for inhibiting tumor growth and angiogenesis and for diagnosing vascular and tumor diseases. Other specifically claimed HMW endostatins include the following:

Glycosylated high-molecular-weight endostatin with a molecular weight of 21.8 kDa

288021

Glycosylated high-molecular-weight endostatin with a molecular weight of 20 kDa

288022

Glycosylated high-molecular-weight endostatin with a molecular weight of 21 kDa

288023

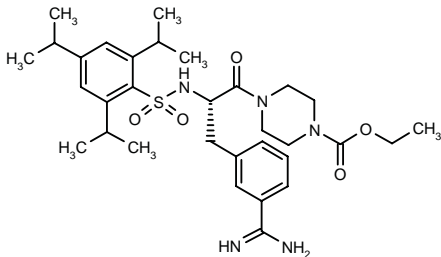
SOURCE – Haemopep.

REFERENCES

1. Ständker, L. and Forssmann, W.-G. (Haemopep Pharma GmbH) *HMW endostatin for inhibiting the growth of tumours and capillary proliferation and for diagnosing vascular and tumour diseases.* WO 0017240.

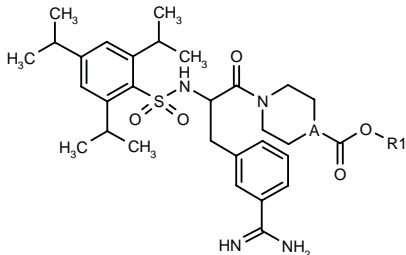
288028

4-[3-(3-Amidinophenyl)-2(S)-(2,4,6-triisopropylphenyl-sulfonamido)propionyl]piperazine-1-carboxylic acid ethyl ester



C32 H47 N5 O5 S; Mol wt: 613.8193

ACTION – Urokinase inhibitor ($K_i = 0.49 \mu\text{M}$) for the treatment and diagnosis of tumors. Other exemplified *N*^α-triisopropylphenylsulfonyl-protected 3-amidinophenyl-alanine derivatives include the following:



Compound	R1	A	Formula
288029	Et	N	C ₃₂ H ₄₇ N ₅ O ₅ S
288030	Et	CH	C ₃₃ H ₄₈ N ₄ O ₅ S
288031	Me	N	C ₃₁ H ₄₅ N ₅ O ₅ S
288032	i-Pr	CH	C ₃₄ H ₅₀ N ₄ O ₅ S

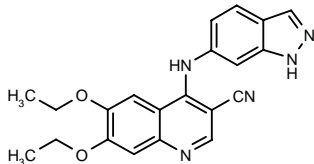
SOURCE – Pentapharm.

REFERENCES

1. Wikström, P. and Vieweg, H. (Pentapharm AG) *Urokinase inhibitors.* WO 0017158.

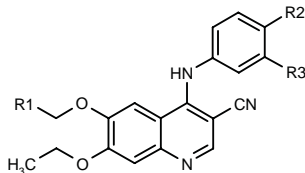
288047

6,7-Diethoxy-4-(1*H*-indazol-6-ylamino)quinoline-3-carbonitrile



C21 H19 N5 O2; Mol wt: 373.4141

ACTION – Antiproliferative agent that acts by inhibiting the protein tyrosine kinase KDR (Kinase insert Domain containing Receptor), implicated in the growth-promoting angiogenic effects of vascular endothelial growth factor (VEGF). The compound is thus expected to be useful in the treatment of angiogenic states such as cancer. It was active *in vitro* against several human cancer cell lines and it inhibited the growth of human colon carcinoma SW620 in mice. When administered at 30 mg/kg i.p. for 20 days, tumor growth was inhibited by 56, 67 and 60% at days 7, 14 and 21, respectively. Other exemplified substituted 3-cyanoquinolines include the following:



Compound	R1	R2	R3	Formula
288048	Me	-CONHCO-		C ₂₂ H ₁₈ N ₄ O ₄
288049	Me	-COCH ₂ CH ₂ -		C ₂₃ H ₂₁ N ₃ O ₃
288050	H	-CH=NNH-		C ₂₀ H ₁₇ N ₅ O ₂

SOURCE – American Home Products.

REFERENCES

1. Wissner, A. et al. (American Cyanamid Co.) *Substd. 3-cyanoquinolines as protein tyrosine kinase inhibitors*. WO 0018761.

12H8 MAb

288667

Murine monoclonal antibody to the Tie2 receptor

ACTION – Tie2 receptor antagonist antibody with potential for inhibiting angiogenesis and thus for the treatment of angiogenic diseases such as cancer, atherosclerosis, psoriasis, arthritis, diabetic retinopathy or macular degeneration. It exhibited high affinity for Tie2 in an immunoassay ($K_D < 0.1$ nM) and was shown to consistently reduce conditioned medium-induced phosphorylation of the Tie2 receptor 60-100% at a maximum concentration of 50 µg/ml. Another specifically claimed antagonist antibody is:

Murine monoclonal antibody to the Tie2 receptor

6A3 MAb [288668]

SOURCE – SmithKline Beecham.

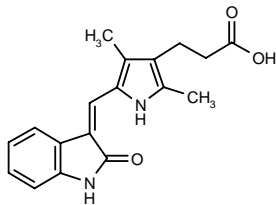
REFERENCES

1. Holmes, S.D. et al. (SmithKline Beecham Corp.;SmithKline Beecham plc) *Tie2 antagonist antibodies*. WO 0018437.

SU-6668*

283644

(Z)-3-[2,4-Dimethyl-5-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidenemethyl)-1*H*-pyrrol-3-yl]propionic acid



C18 H18 N2 O3; Mol wt: 310.3512

ACTION – Antineoplastic agent, a potent and broad-spectrum inhibitor of vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinases ($IC_{50} = 0.02, 1.3$ and 0.06 µM, respectively). In mice bearing colon cancer CT-26 tumors, compound (60 mg/kg/day i.p.) strongly inhibited liver metastases (55.3%), the formation of microvessels (36.2%) and tumor cell proliferation (27.3%), and it increased tumor cell and endothelial cell apoptosis. Currently undergoing phase I studies for the treatment of solid tumors.

SOURCE – Sugen.

REFERENCES

1. Tang, P.C. et al. (Sugen, Inc.) *Pyrrole substd. 2-indolinone protein kinase inhibitors*. WO 9961422.

2. Chanda, S.M. et al. *SU5416 and SU6668: Comparative differences in toxicity profile in rats following intravenous administration*. Proc Amer Assoc Cancer Res 2000, 41: Abst 4470.

3. Laird, A.D. et al. *SU6668, a broad spectrum angiogenesis inhibitor, exhibits potent anti-tumor activity in xenograft models, including regression of established tumors*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 410.

4. Laird, D. et al. *SU6668, a broad spectrum angiogenesis inhibitor, exhibits potent activity against established tumors in diverse mouse xenograft models*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3615.

5. Liang, C. et al. *Discovery and design of angiogenesis inhibitors that inhibit tyrosine kinase activities associated with VEGF, FGF, and PDGF receptors*. Proc Amer Assoc Cancer Res 1999, 40: Abst 452.

6. Miyadera, K. et al. *Pharmacological evaluation of a novel receptor tyrosine kinase inhibitor, SU006668, exhibiting a strong in vivo antitumor activity*. Proc Amer Assoc Cancer Res 2000, 41: Abst 2841.

7. Rosen, L. et al. *Phase I dose-escalating trial of oral SU006668, a novel multiple receptor tyrosine kinase inhibitor in patients with selected advanced malignancies*. Proc Am Soc Clin Oncol 2000, 19: Abst 708.

8. Shaheen, R.M. et al. *Antiangiogenic therapy targeting the tyrosine kinase receptor for vascular endothelial growth factor receptor inhibits the growth of colon cancer liver metastasis and induces tumor and endothelial cell apoptosis*. Cancer Res 1999, 59(21): 5412.

9. Shawver, L.K. et al. *SU6668 is a potent, broad spectrum angiogenesis inhibitor that exhibits anti-tumor properties*. Proc Amer Assoc Cancer Res 1999, 40: Abst 4777.

10. Smolich, B.D. et al. *SU5416 and SU6668 inhibit biochemical and biological functions of c-kit*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3083.

11. Sukbuntherng, J. et al. *Comparison of the disposition kinetics of specific, SU5416, and broad acting, SU6668, angiogenesis inhibitors*. Proc Amer Assoc Cancer Res 2000, 41: Abst 5175.

12. Tang, C. et al. *Design, synthesis, and evaluation of substituted 3-[(3-or 4-carboxyethylpyrrol-2-yl)methylindenyl]indolin-2-ones as inhibitors of VEGF, PDGF, and FGF receptor tyrosine kinases*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 18.

13. Vajkoczy, P. et al. *Targeting VEGF, FGF, and PDGF receptors with SU6668: Effects on tumor growth, angiogenesis, and microcirculation*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3612.

14. Yonekura, K. et al. *A novel angiogenesis inhibitor, SU0006668, strongly exhibiting in vivo anticancer activity*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3609.

15. Yorozuya, K. et al. *SU6668 inhibits the growth of human colon carcinoma xenografts transplanted into severe combined immunodeficient mouse*. Proc Amer Assoc Cancer Res 2000, 41: Abst 1101.

16. *New anticancer drug candidate revealed by Sugen; product enters phase I testing in U.K.* DailyDrugNews.com (Daily Essentials) 1998, Nov 11.

17. *Sugen announces breakthrough in development of cytostatic anti-cancer agents with new drug, SU6668*. Sugen, Inc. Press Release 1998, Nov 10.

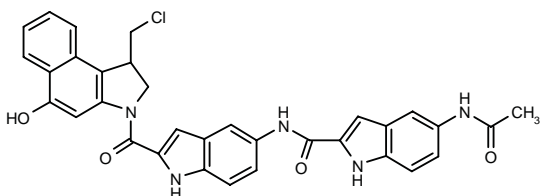
18. *U.S. clinical trials of SU-6668 slated for early 1999*. DailyDrugNews.com (Daily Essentials) 1998, Dec 29.

*Identified compound **283644** Drug Data Rep 2000, 022(01): 0087.

OTHER ONCOLYTIC DRUGS

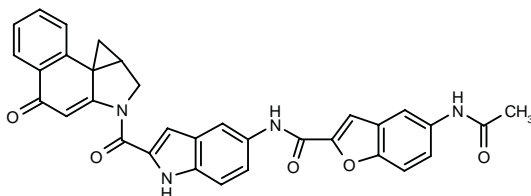
286879^{1,2}

5-(Acetamido)-*N*-[2-[1-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benzo[*e*]indol-3-ylcarbonyl]-1*H*-indol-5-yl]-1*H*-indole-2-carboxamide



C33 H26 Cl N5 O4; Mol wt: 592.0524

ACTION – Antineoplastic agent, an analogue of CC-1065 with *in vitro* cytotoxic activity against all human cancer cell lines tested in the NCI *in vitro* screen, giving IC₅₀ values in the range 0.1-5 nM for most cell lines. The mechanism of tumor cell death was via induction of apoptosis. *In vivo* in mice bearing leukemia L1210, compound at a dose of 70 µg/kg i.p. induced a 107% increase in life span, and was much more active than cyclophosphamide. It was also active in mice bearing melanoma B16BL6 and did not induce myelosuppression at therapeutically effective doses. Another related compound is:



286880: C33 H24 N4 O5

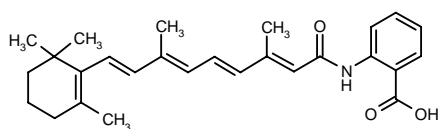
SOURCE – Panorama Research.

REFERENCES

1. Wang, Y. et al. (Panorama Research, Inc.) *DNA-binding indole derivs., their prodrugs and immunoconjugates as anticancer agents*. WO 9744000.
2. Wang, Y. et al. *Synthesis and preliminary biological evaluations of CC-1065 analogues: Effects of different linkers and terminal amides on biological activity*. J Med Chem 2000, 43(8): 1541.

287224

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2(*E*),4(*E*),6(*E*),8(*E*)-nonatetraenamido]benzoic acid



C27 H33 N O3; Mol wt: 419.5617

ACTION – Antineoplastic agent, a structural derivative of the retinamide fenretinide shown to be at least as effective as the parent compound against certain lung and head and neck cancer cell lines (IC₅₀ < 0.8 µM). Furthermore, whereas fenretinide failed to induce apoptosis, compound exhibited apoptotic activity at concentrations of about 1 µM. Considered a good candidate for further evaluation as a potential chemopreventive or cancer therapeutic.

SOURCES – M.D. Anderson Cancer Center, Houston, TX (US); National Cancer Institute, Bethesda, MD (US).

REFERENCES

1. Yue, P. et al. *Identification of retinamides that are more potent than N-(4-hydroxyphenyl)retinamide (4HPR) in inhibiting the growth of human head and neck and lung cancer cells*. Proc Amer Assoc Cancer Res 2000, 41: Abst 352.

287411

Monoclonal antibody to human protein OZF

ACTION – Monoclonal antibody against the human protein OZF (only zinc fingers) with potential in the treatment, prevention or diagnosis of pathologies associated with abnormal OZF protein expression such as cancer, particularly pancreatic, colon or breast cancer.

SOURCES – CNRS; Institut Curie, Paris (FR).

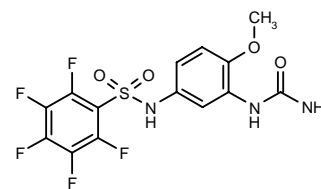
REFERENCES

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287750

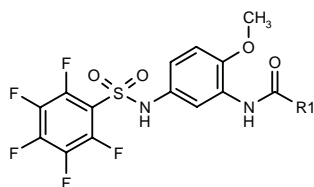
N-(4-Methoxy-3-ureidophenyl)perfluorobenzenesulfonamide

N-[2-Methoxy-4-(pentafluorobenzenesulfonamido)phenyl]urea



C14 H10 F5 N3 O4 S; Mol wt: 411.3060

ACTION – Antiproliferative agent proven to inhibit abnormal cell proliferation and to lower plasma cholesterol levels. *In vitro*, it inhibited cell growth of human cervical adenocarcinoma HeLa cells and human breast cancer MCF-7/ADR cells, with complete growth inhibition at < 5 µM. It may have potential utility in the treatment of proliferative diseases such as cancer, psoriasis, vascular restenosis or infections, and hypercholesterolemia. Other exemplified arylsulfonamide ureas include the following:



Compound	R1	Formula
287751	5-NH2-1-pyrazolyl	C ₁₇ H ₁₂ F ₅ N ₅ O ₄ S
287752	2-furyl-CH2NH	C ₁₉ H ₁₄ F ₅ N ₃ O ₅ S
287753	5-NH2-1,2,4-triazol-1-yl	C ₁₆ H ₁₁ F ₅ N ₆ O ₄ S

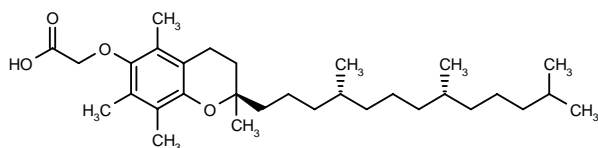
SOURCE – Tularik.

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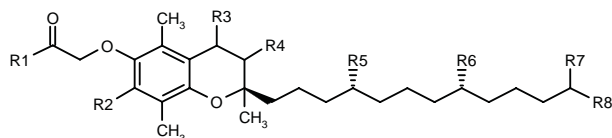
287767

2-[2(*R*),5,7,8-Tetramethyl-2-[4(*R*),8(*R*),12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-yloxy]acetic acid

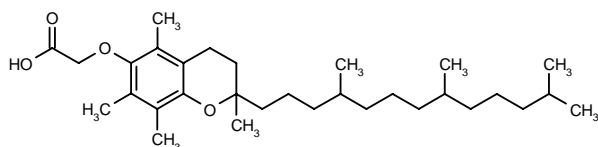


C31 H52 O4; Mol wt: 488.7478

ACTION – Apoptosis-inducing and antiproliferative agent found to induce apoptosis in a wide variety of human cancer cells including breast cancer (MDA-MB-435, MDA-MB-231 and MCF-7), prostate cancer (PC-3, DU-125 and LnCap), cervical tumor (ME-180), ovarian tumor (C-170) and endometrial cancer cells (RL-95-2), without inducing apoptosis in normal human mammary epithelial cells (HMECs). It has been shown to activate the Fas/Fas ligand apoptotic signaling pathway in Fas signaling-resistant cancer cells and to arrest DNA synthesis in human breast cancer MDA-MB-435 cells. Other exemplified compounds from this series of chroman derivatives are:



Compound	R1	R2	R3	R4	R5=R6=R7	R8	Formula
287769	OH	H	H		Me	H	C ₃₀ H ₅₀ O ₄
287770	N(CH ₂ CO ₂ H) ₂	Me	H		Me	H	C ₃₅ H ₅₇ NO ₇
287774	OH	Me	bond		Me	H	C ₃₁ H ₅₀ O ₄
287775	OH	Me	H		H	Bu	C ₃₂ H ₅₄ O ₄



287773: C31 H52 O4

SOURCE – Research Development Foundation.

REFERENCES

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ANVIRZEL™

287673

Hot water extract of Nerium oleander containing oleandrin and its alkycone oleandrigenin

ACTION – Antineoplastic agent extracted from the plant *Nerium oleander* whose cytotoxic components were identified as oleandrin and its aglycone oleandrogenin. Oleandrin displayed potent cytotoxicity against human melanoma BRO cells ($IC_{50} = 3.0$ ng/ml), but was ineffective against murine melanoma B16. In human prostate cancer cells, oleandrin was shown to block the release of basic fibroblast growth factor (bFGF), increase intracellular Ca^{2+} levels and induce mitochondrial release of cytochrome C and apoptosis, effects which appeared to involve Na^+/K^+ -ATPase inhibition.

SOURCE – Ozelle.

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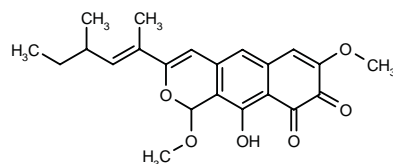
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EC-1007

287380

3-[1,3-Dimethyl-1(*E*)-pentenyl]-10-hydroxy-1,7-dimethoxy-1*H*-naphtho[2,3-*c*]pyran-8,9-dione



C22 H24 O6; Mol wt: 384.4256

ACTION – Antineoplastic agent isolated from *Trichocladium* sp. EC1007 (FERM BP-6439), shown to inhibit the proliferation of human colon adenocarcinoma WiDr cells ($IC_{50} = 1.1 \mu M$). In addition, compound exhibited moderate antibacterial activity against *Staphylococcus aureus* ATCC6538P (MIC = 10.4 $\mu g/ml$), *Enterococcus hirae* ATCC10541 (MIC = 5.2 $\mu g/ml$) and *Bacillus subtilis* No. 10707 (MIC = 5.2 $\mu g/ml$).

SOURCE – Kyowa Hakko.

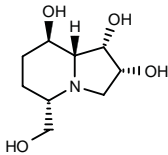
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GD-46

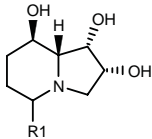
288011

(1*S*,2*R*,5*S*,8*R*,8*aR*)-5-(Hydroxymethyl)perhydroindolizine-1,2,8-triol



C9 H17 N O4; Mol wt: 203.2363

ACTION – Immunostimulant, a swainsonine analogue for the treatment of proliferative disorders and microbial infections shown to produce significant inhibition of Golgi α -mannosidase II activity relative to lysosomal mannosidase activity (IC_{50} = 0.638 \pm 0.22 and 1.485 \pm 0.455 μ M, respectively), and thus expected to be devoid of the side effects exhibited by swainsonine. This compound is particularly useful in the prevention of tumor recurrence after surgery. Other compounds from this series of 3, 5 and/or 6-substituted swainsonine analogues are:



Compound	R1	Isomer	Formula
GD-28 [288012]	Me	S	C ₉ H ₁₇ NO ₃
GD-38 [288014]	Et	S	C ₁₀ H ₁₉ NO ₃
GD-91 [288015]	CH ₂ OCH ₂ Ph	S	C ₁₆ H ₂₃ NO ₄
GD-42 [288016]	CH ₂ OCH ₂ Ph	R	C ₁₆ H ₂₃ NO ₄

SOURCE – GlycoDesign.

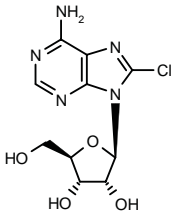
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NSC-354258

274911

8-Chloroadenosine



C10 H12 Cl N5 O4; Mol wt: 301.6888

ACTION – Antineoplastic agent, a dephosphorylated metabolite of 8-chloro-cAMP proven to induce growth inhibition in human leukemia HL-60 and K-562 cells and human gastric cancer MGc80-3 cells (IC_{50} = 1.8, 4.2 and 1.56 μ M, respectively), and against human adenocarcinoma HCT 116 and FET cell lines (IC_{50} = 1.3 and 2.0 μ M, respectively). In HL-60 cells, compound was shown to arrest cells in the G0/G1 phase and to inhibit the

expression of both cyclin D1 and *c-myc*, as well as to suppress telomerase activity. At a dose of 100 mg/kg/day i.p. for 7 days, it exhibited strong antitumor activity in mice bearing hepatoma 22 (71.7% inhibition) and ascitic leukemia L1210 (124% increase in survival rate). Toxicity studies in dogs demonstrated that compound did not produce the nephrotoxicity and hypercalcemia characteristic of 8-chloro-cAMP.

SOURCES – Beijing Medical University, Beijing (CN); National Cancer Institute, Bethesda, MD (US).

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CANCER GENE THERAPY

ONYX-015

235381

Chimeric human group C adenovirus (Ad2 and Ad5) that has a deletion between nucleotides 2496 and 3323 in the EB1 region encoding the 55-kDa protein. In addition, there is a C-to-T transition in position 2022 that generates a stop codon at the third codon position of the protein

CI-1042
Ad5-d11520
d11520

ACTION – Antineoplastic agent, a genetically modified, replication-deficient adenovirus shown in preclinical and clinical studies to selectively replicate in and kill tumor cells deficient in p53 tumor suppressor gene activity. Compound produced complete cytolysis in p53-deficient brain, breast, colon, cervix, larynx, liver, lung, ovary, pancreas and prostate tumor cells, whereas its replication in normal p53+ endothelial and epithelial cells was significantly attenuated, giving a therapeutic index of 100-1,000. In nude mice bearing several p53-deficient tumor xenografts, compound given intratumorally induced over 50% complete regression of p53-deficient cervical carcinoma (C33A) over 6 months. In a liver metastasis model in animals injected with colon carcinoma HT-29 cells, compound induced 50% reduction in liver metastases at 3 and 5 weeks, and a significant reduction in both the number and size of tumors was observed in animals developing metastases. Another preclinical study demonstrated increased efficacy of compound when administered in combination with cisplatin *in vitro* and *in vivo*. Phase I and II clinical studies demonstrated the efficacy of compound against head and neck cancer, ovarian, pancreatic and Barrett's esophageal cancer, as well as against liver metastases from colon cancer. Phase III clinical trials in patients with recurrent and refractory head and neck cancer were recently commenced.

SOURCES – Onyx; Pfizer.

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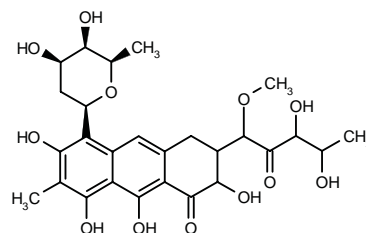
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

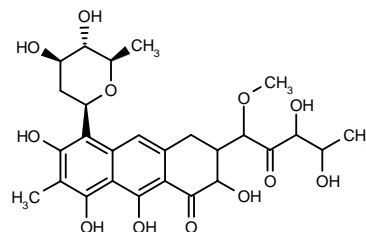
288135

3-(3,4-Dihydroxy-1-methoxy-2-oxopentyl)-5-(2,6-dideoxy-β-D-galactopyranosyl)-2,6,8,9-tetrahydroxy-7-methyl-1,2,3,4-tetrahydroanthracen-1-one



C27 H34 O12; Mol wt: 550.5536

ACTION – Inhibitor of multidrug resistance MDR1 gene expression extracted from a culture broth of *Streptomyces* sp. KS12571. In human small cell lung cancer SBC-3/ADM cells, compound inhibited MDR1 gene expression in a concentration-dependent manner (0.1-0.6 mg/ml). Another related aryl C-glycoside is:



288136: C27 H34 O12

SOURCE – Asahi Breweries.

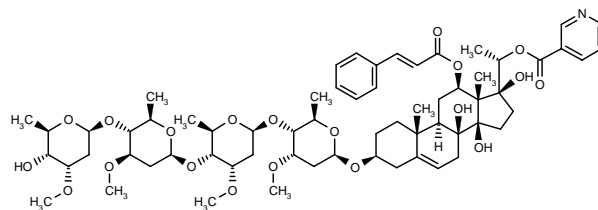
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CW-1

287677

3β-[O-2,6-Dideoxy-3-O-methyl-β-D-allopyranosyl-(1→4)-O-2,6-dideoxy-3-O-methyl-β-D-mannopyranosyl-(1→4)-O-2,6-dideoxy-3-O-methyl-β-D-allopyranosyl-(1→4)-2,6-dideoxy-3-O-methyl-β-D-allopyranosyloxy]-12β-[3-phenyl-2(E)-propenoyloxy]-20(S)-(3-pyridylcarbonyloxy)pregn-5-ene-8β,14β,17β-triol



C64 H91 N O20; Mol wt: 1194.4100

White amorphous powder, m.p. 185-7 °C; [α]_D²⁵ +20.0° (c 0.5, MeOH).

ACTION – Multidrug resistance-reversing agent extracted from the roots of *Cynanchum wilfordii*, able to completely reverse multidrug resistance of human oral epidermoid cancer KB-V1 cells and human breast cancer MCF-7/ADR cells to vinblastine, doxorubicin and colchicine at a concentration of 1 μ M. In addition, compound strongly inhibited basic fibroblast growth factor (bFGF)-induced angiogenesis in a chorioallantoic membrane assay and a Matrigel plug assay.

SOURCES – Korea Research Institute of Bioscience and Biotechnology, Taedok Science Town (KR); Pusan National University, Pusan (KR).

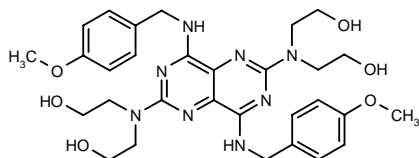
REFERENCES

1. Hwang, B.Y. et al. *Pregnane glycoside multidrug-resistance modulators from Cynanchum wilfordii*. J Nat Prod 1999, 62(4): 640.
2. Lee, J. et al. *Multidrug resistance reversing and antiangiogenic activity of pregnane glycosides from Cynanchum wilfordii*. Proc Amer Assoc Cancer Res 2000, 41: Abst 4776.
3. Warashina, T. and Noro, T. *Steroidal glycosides from roots of Cynanchum caudatum*. III.. Chem Pharm Bull 1999, 44(2): 358.

NU-3076

234468

2,2',2'',2'''-[4,8-Bis(4-methoxybenzylamino)pyrimido-[5,4-d]pyrimidine-2,6-diyl]bis(nitrilo)tetrakis(ethanol)



C30 H40 N8 O6; Mol wt: 608.6960

ACTION – Antineoplastic agent, an analogue of dipyradamole proven to enhance the *in vitro* activity of antimetabolite anticancer drugs through inhibition of nucleoside transport. Compound was able to block thymidine uptake in murine leukemia L1210 cells ($K_i = 0.1 \mu$ M) and its activity was not significantly affected by the plasma protein α_1 -acid glycoprotein (AGP), which completely abolished the activity of dipyradamole. Although it was not cytotoxic *per se* against murine leukemia L1210 cells, it was able to enhance the growth-inhibitory activity of the antifolate thymidylate synthase inhibitors CB-3717 and nolatrexed, and 5-fluorouracil.

SOURCE – University of Newcastle upon Tyne, Newcastle upon Tyne (GB).

REFERENCES

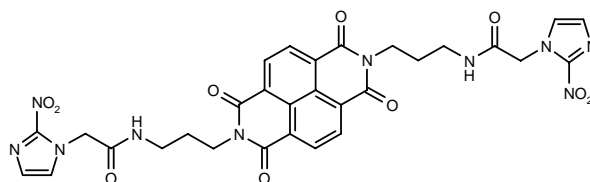
1. Griffin, R.J. et al. (University of Newcastle upon Tyne) *Pyrimidopyrimidine cpds*. WO 9843974.
2. Barlow, H.C. et al. *Resistance-modifying agents. Part 7: 2,6-Disubstituted-4,8-dibenzylaminopyrimido[5,4-d]pyrimidines that inhibit nucleoside transport in the presence of α_1 -acid glycoprotein (AGP)*. Bioorg Med Chem Lett 2000, 10(6): 585.
3. Curtin, N.J. et al. *Potentiation of the cytotoxicity of thymidylate synthase (TS) inhibitors by dipyradamole analogues with reduced α_1 -acid glycoprotein binding*. Br J Cancer 1999, 80(11): 1738.
4. Loughlin, P. et al. *Novel analogues of dipyradamole which retain nucleoside transport inhibitory potency in the presence of α_1 acid glycoprotein*. 9th NCI-EORTC Symp New Drugs Cancer Ther (March 12-15, Amsterdam) 1996, Abst 415.

RADIOSENSITIZERS

TX-1932

287733

2,7-Bis[3-(2-nitro-1*H*-imidazol-1-ylacetamido)propyl]-1,3,6,8-tetraoxo-1,3,6,8-tetrahydrobenzo[*lmn*][3,8]-phenanthroline



C30 H26 N10 O10; Mol wt: 686.5954

ACTION – Antineoplastic agent and hypoxic cell radiosensitizer with antiproliferative activity in a clonogenic assay in EMT6/KU cells ($IC_{50} = 29 \mu$ M) and reported to bind with high affinity to double-stranded DNA.

SOURCE – University of Tokushima, Tokushima (JP).

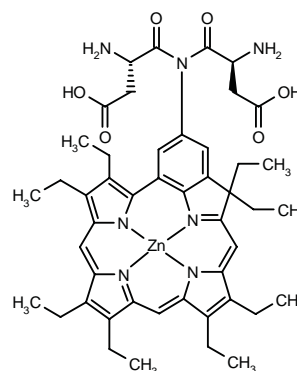
REFERENCES

1. Utsu, Y. et al. *Molecular design of TX-1932 a hypoxic cell radiosensitizer with potential anticancer activity*. 120th Annu Meet Pharm Soc Jpn (March 29-31, Gifu) 2000, Abst 30-PB-12-47.

PHOTOSENSITIZERS

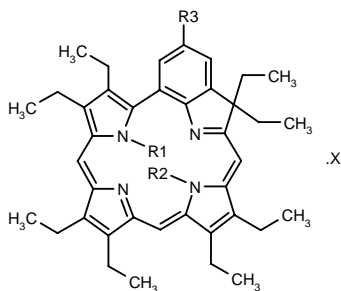
288451

[2²-[*N,N*-Bis(L-aspartyl)amino]-3,3,7,8,12,13,17,18-octaethyl-3*H*-benzo[*a*]porphyrinato(2-)]zinc

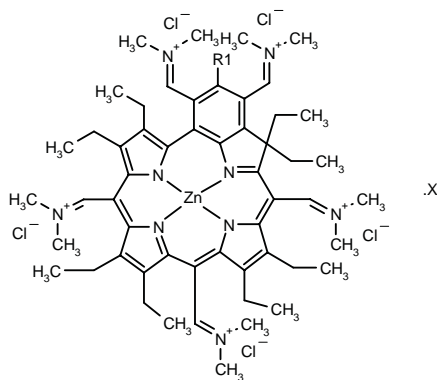


C47 H57 N7 O6 Zn; Mol wt: 881.4003

ACTION – Photosensitizer for use in the photodynamic therapy of tumors, shown to provide more potent cytotoxic responses than Photofrin® (porfimer sodium) when administered to mice bearing RIF tumors at 2.5 mg/kg i.v. followed by light irradiation (100 and 30% response at 7 and 30 days posttreatment, respectively, vs. 40 and 0% response, respectively for Photofrin®). Other exemplified compounds from this series of benzochlorin derivatives include the following:



Compound	R1	R2	R3	X	Formula
288452	H	H	Br		C ₃₉ H ₄₇ BrN ₄
288453	-Zn-		Br		C ₃₉ H ₄₅ BrN ₄ Zn
288454	-Zn-		NO ₂		C ₃₉ H ₄₅ N ₅ O ₂ Zn
288455	H	H	NH ₂		C ₃₉ H ₄₉ N ₅
288456	H	H	N(Me) ₃ ⁺	iodide	C ₄₂ H ₅₆ IN ₅



Compound	R1	R2	X	Formula
288457	Br			C ₆₄ H ₇₅ BrCl ₅ N ₉ Zn
288458	NH+Me ₂		Cl	C ₅₆ H ₈₂ Cl ₆ N ₁₀ Zn

SOURCE – Lambda Pharmaceuticals.

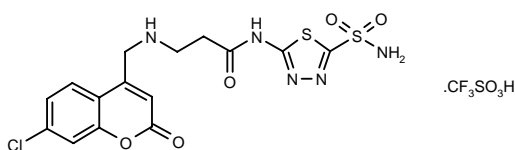
REFERENCES

1. Morgan, A.R. et al. (Lambda Pharmaceuticals, Inc.) *Photosensitizers for photodynamic application*. WO 0020419.

OCULAR MEDICATIONS

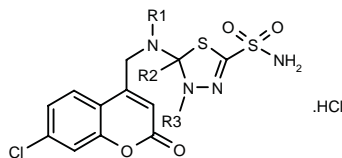
288825

5-[3-(7-Chloro-2-oxo-2*H*-1-benzopyran-4-ylmethyl-amino)propanamido]-1,3,4-thiadiazole-2-sulfonamide trifluoromethanesulfonate

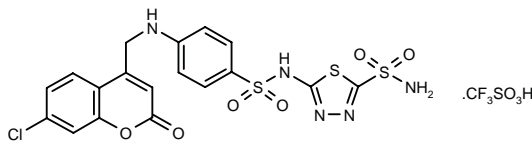


C15 H14 Cl N5 O5 S2 . C H F3 O3 S; Mol wt: 593.9665

ACTION – Antiglaucoma agent, a water-soluble inhibitor of carbonic anhydrase (CA; K_i = 2, 12 and 16 nM against human CA II, human CA I and bovine CA IV, respectively). Compound was much more effective than dorzolamide in lowering intraocular pressure in normotensive rabbits after topical administration of a 2% solution, with a long duration of action (5-6 h). Other representative compounds from this series of coumarin derivatives are:



Compound	R1	R2	R3	Formula
288495	H	bond		C ₁₂ H ₉ ClN ₄ O ₄ S ₂ .HCl
288496	bond		Me	C ₁₃ H ₁₁ ClN ₄ O ₄ S ₂ .HCl



288497: C18 H14 Cl N5 O6 S3 . C H F3 O3 S

SOURCE – Università degli Studi di Firenze, Firenze (IT).

REFERENCES

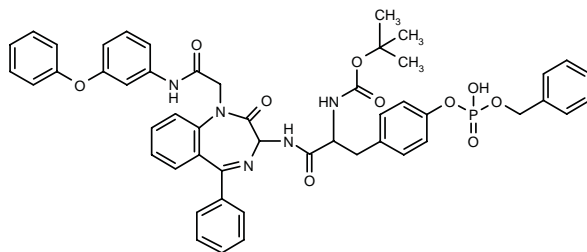
1. Renzi, G. et al. *Carbonic anhydrase inhibitors: Topical sulfonamide antiglaucoma agents incorporating secondary amine moieties*. *Bioorg Med Chem Lett* 2000, 10(7): 673.

METABOLIC DRUGS

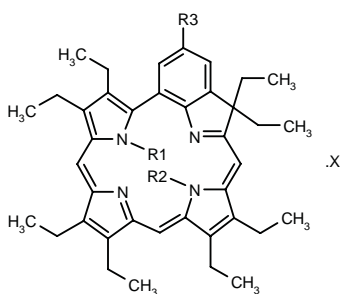
TREATMENT OF BONE DISEASES

287282

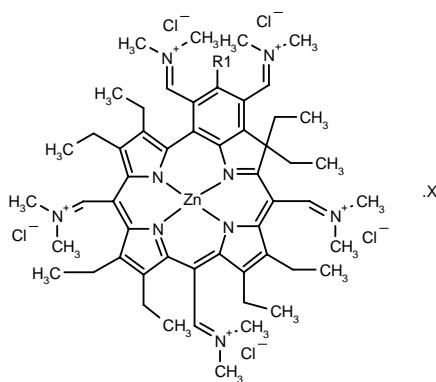
N-[2-[4-((Benzyloxy)(hydroxy)phosphoryloxy)phenyl]-1-[N-[2-oxo-1-[N-(3-phenoxyphenyl)carbamoylmethyl]-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-3-ylcarbamoyl]ethyl]carbamic acid *tert*-butyl ester enantiomer B



C50 H48 N5 O10 P; Mol wt: 909.9282



Compound	R1	R2	R3	X	Formula
288452	H	H	Br		C ₃₉ H ₄₇ BrN ₄
288453	-Zn-		Br		C ₃₉ H ₄₅ BrN ₄ Zn
288454	-Zn-		NO ₂		C ₃₉ H ₄₅ N ₅ O ₂ Zn
288455	H	H	NH ₂		C ₃₉ H ₄₉ N ₅
288456	H	H	N(Me) ₃ +	iodide	C ₄₂ H ₅₆ N ₅



Compound	R1	R2	X	Formula
288457	Br			C ₅₄ H ₇₅ BrCl ₆ N ₉ Zn
288458	NH+Me ₂		Cl	C ₉₆ H ₈₂ Cl ₆ N ₁₀ Zn

SOURCE – Lambda Pharmaceuticals.

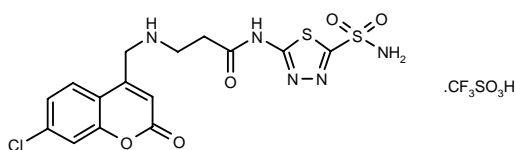
REFERENCES

1. Morgan, A.R. et al. (Lambda Pharmaceuticals, Inc.) *Photosensitizers for photodynamic application*. WO 0020419.

OCULAR MEDICATIONS

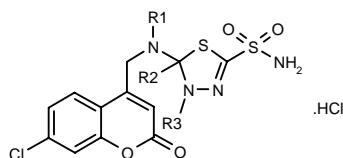
288825

5-[3-(7-Chloro-2-oxo-2*H*-1-benzopyran-4-ylmethylamino)propanamido]-1,3,4-thiadiazole-2-sulfonamide trifluoromethanesulfonate

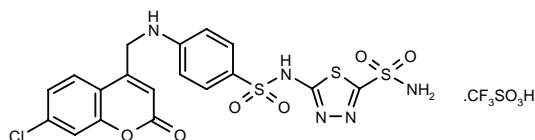


C15 H14 Cl N5 O5 S2 . C H F3 O3 S; Mol wt: 593.9665

ACTION – Antiglaucoma agent, a water-soluble inhibitor of carbonic anhydrase (CA; K_i = 2, 12 and 16 nM against human CA II, human CA I and bovine CA IV, respectively). Compound was much more effective than dorzolamide in lowering intraocular pressure in normotensive rabbits after topical administration of a 2% solution, with a long duration of action (5-6 h). Other representative compounds from this series of coumarin derivatives are:



Compound	R1	R2	R3	Formula
288495	H	bond		C ₁₂ H ₉ ClN ₄ O ₄ S ₂ .HCl
288496	bond		Me	C ₁₃ H ₁₁ ClN ₄ O ₄ S ₂ .HCl



288497: C18 H14 Cl N5 O6 S3 . C H F3 O3 S

SOURCE – Università degli Studi di Firenze, Firenze (IT).

REFERENCES

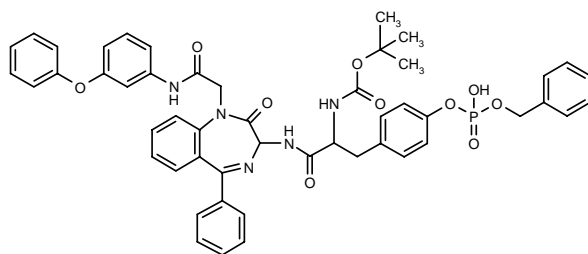
1. Renzi, G. et al. *Carbonic anhydrase inhibitors: Topical sulfonamide antiglaucoma agents incorporating secondary amine moieties*. *Bioorg Med Chem Lett* 2000, 10(7): 673.

METABOLIC DRUGS

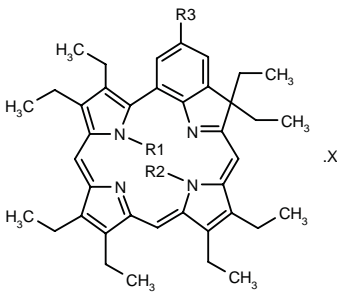
TREATMENT OF BONE DISEASES

287282

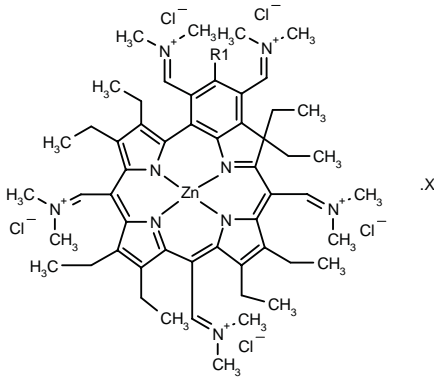
N-[2-[4-[(Benzyloxy)(hydroxy)phosphoryloxy]phenyl]-1-[*N*-[2-oxo-1-[*N*-(3-phenoxyphenyl)carbamoylmethyl]-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-3-ylcarbamoyl]ethyl]carbamic acid *tert*-butyl ester enantiomer B



C50 H48 N5 O10 P; Mol wt: 909.9282



Compound	R1	R2	R3	X	Formula
288452	H	H	Br		C ₃₉ H ₄₇ BrN ₄
288453	-Zn-		Br		C ₃₉ H ₄₅ BrN ₄ Zn
288454	-Zn-		NO ₂		C ₃₉ H ₄₅ N ₅ O ₂ Zn
288455	H	H	NH ₂		C ₃₉ H ₄₉ N ₅
288456	H	H	N(Me) ₃ ⁺	iodide	C ₄₂ H ₅₆ IN ₅



Compound	R1	R2	X	Formula
288457	Br			C ₅₄ H ₇₅ BrCl ₅ N ₉ Zn
288458	NH+Me ₂		Cl	C ₅₆ H ₈₂ Cl ₆ N ₁₀ Zn

SOURCE – Lambda Pharmaceuticals.

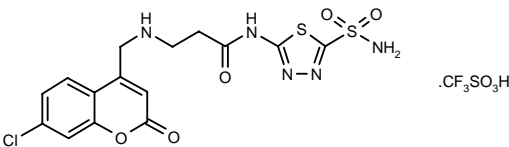
REFERENCES

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OCULAR MEDICATIONS

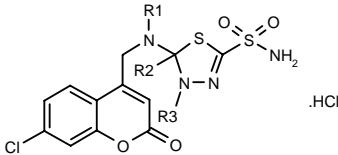
288825

5-[3-(7-Chloro-2-oxo-2*H*-1-benzopyran-4-ylmethyl-amino)propanamido]-1,3,4-thiadiazole-2-sulfonamide tri-fluoromethanesulfonate

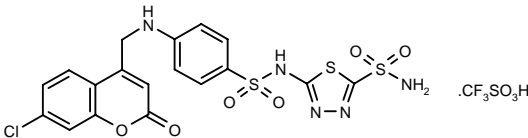


C15 H14 Cl N5 O5 S2 . C H F3 O3 S; Mol wt: 593.9665

ACTION – Antiglaucoma agent, a water-soluble inhibitor of carbonic anhydrase (CA; K_i = 2, 12 and 16 nM against human CA II, human CA I and bovine CA IV, respectively). Compound was much more effective than dorzolamide in lowering intraocular pressure in normotensive rabbits after topical administration of a 2% solution, with a long duration of action (5-6 h). Other representative compounds from this series of coumarin derivatives are:



Compound	R1	R2	R3	Formula
288495	H	bond		C ₁₂ H ₉ ClN ₄ O ₄ S ₂ .HCl
288496	bond		Me	C ₁₃ H ₁₁ ClN ₄ O ₄ S ₂ .HCl



288497: C18 H14 Cl N5 O6 S3 . C H F3 O3 S

SOURCE – Università degli Studi di Firenze, Firenze (IT).

REFERENCES

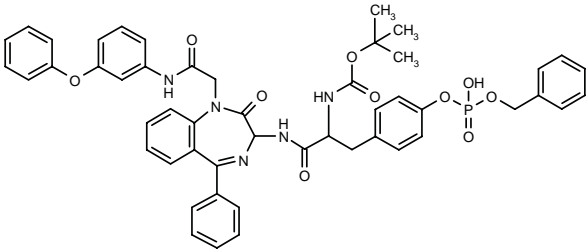
1. Renzi, G. et al. *Carbonic anhydrase inhibitors: Topical sulfonamide antiglaucoma agents incorporating secondary amine moieties*. Bioorg Med Chem Lett 2000, 10(7): 673.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

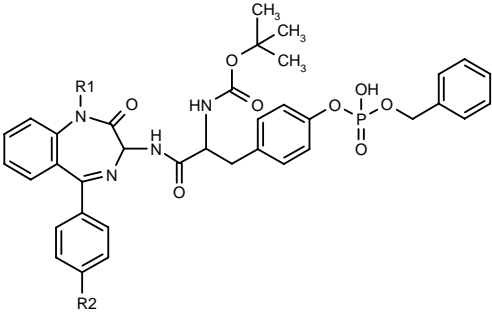
287282

N-[2-[4-[(Benzyloxy)(hydroxy)phosphoryloxy]phenyl]-1-[*N*-[2-oxo-1-[*N*-(3-phenoxyphenyl)carbamoylethyl]-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-3-ylcarbamoylethyl]carbamic acid *tert*-butyl ester enantiomer B

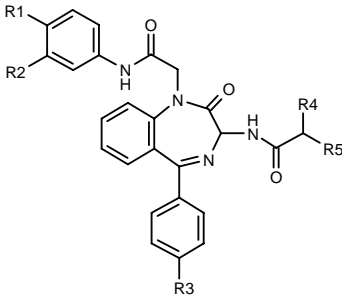


C50 H48 N5 O10 P; Mol wt: 909.9282

ACTION – Agent for the treatment or prevention of disorders characterized by bone loss, notably osteoporosis, hypercalcemia of malignancy, osteopenia due to bone metastases or immobilization, hyperparathyroidism, rheumatoid arthritis and Paget’s disease, with inhibitory activity against Src protein tyrosine kinase at the level of the SH2 domain, as demonstrated in a scintillation proximity assay (IC₅₀ = 7 µmol). Other compounds from this series of benzodiazepinone derivatives include the following:



Compound	R1	R2	Isomer	Formula
287283	3-(PhO)-PhNHCOCH2	H		C ₅₀ H ₄₈ N ₅ O ₁₀ P
287284	3-(PhO)-PhNHCOCH2	H	A	C ₅₀ H ₄₈ N ₅ O ₁₀ P
287285	H	cyclohexyl-CH2OCO		C ₄₄ H ₄₉ N ₄ O ₁₀ P



Compound	R1	R2	R3	R4	R5	Formula
287286	PhO	H	t-BuOCONH	4-(H2PO3O)-Ph	H	C ₄₂ H ₄₀ N ₅ O ₁₀ P
287287	PhO	H	NH2	4-(H2PO3O)-Ph	H	C ₃₇ H ₃₂ N ₅ O ₈ P
287288	H	PhO	CO2H	t-BuOCONH	H	C ₃₇ H ₃₈ N ₅ O ₈
287289	H	PhO	CO2H	4-(H2PO3O)-PhCH2	NH2	C ₃₉ H ₃₄ N ₅ O ₁₀ P

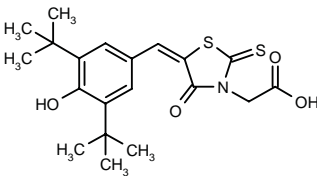
SOURCE – Aventis Pharma.

REFERENCES

1. Deprez, P. et al. (Aventis Pharma SA) *Benzodiazepinone derivs., preparation method and intermediates therefor, use as medicines and compsns.* FR 2782997, WO 0014073.

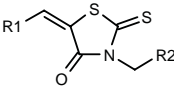
288040

2-[5-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl]acetic acid



C20 H25 N O4 S2; Mol wt: 407.5525

ACTION – Bone regeneration enhancer found to stimulate parathyroid hormone (PTH) receptor-mediated adenylate cyclase (cAMP) formation and thus especially useful for osteopenic disorders such as osteoporosis, rheumatoid arthritis, osteoarthritis and degenerative arthrosis, and as a bone regeneration adjuvant in orthopedic indications, in fracture healing or for healing of bone implants. Other exemplified rhodanine carboxylic acid derivatives are:



Compound	R1	R2	Formula
288043	2,6,6-(Me)3-1-cyclohexen-1-yl- -CH=CHC(Me)=CH	CO2H	C ₂₀ H ₂₆ NO ₃ S ₂
288044	4-OH-3,5-(t-Bu)2-Ph	CH2CO2H	C ₂₁ H ₂₇ NO ₄ S ₂

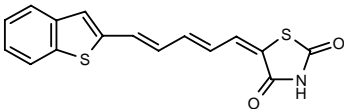
SOURCE – Roche Diagnostics.

REFERENCES

1. Esswein, A. et al. (Roche Diagnostics GmbH) *Rhodanine carboxylic acid derivs. for the treatment and prevention of metabolic bone disorders.* WO 0018747.

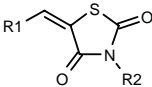
288113

5-[5-(Benzothien-2-yl)penta-2,4-dienylidene]thiazol-idine-2,4-dione



C16 H11 N O2 S2; Mol wt: 313.3999

ACTION – Agent with the ability to stimulate parathyroid hormone (PTH) receptor-mediated adenylate cyclase (cAMP) formation, useful for the treatment and prevention of metabolic bone disorders, particularly for the local or systemic treatment of osteoporosis, rheumatoid arthritis, osteoarthritis and degenerative arthrosis. Other exemplified thiazolidine derivatives are:



Compound	R1	R2	Formula
288115	2-benzothienyl-CH=CH	H	C ₁₄ H ₉ NO ₂ S ₂
288117	4-OH-3,5-(t-Bu)2-Ph	CH2CO2H	C ₂₀ H ₂₅ NO ₅ S
288119	2,6,6-(Me)3-1-cyclohexen-1-yl- -CH=CHC(Me)=CH	CH2CO2H	C ₂₀ H ₂₅ NO ₄ S

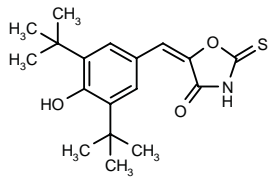
SOURCE – Roche Diagnostics.

REFERENCES

1. Esswein, A. et al. (Roche Diagnostics GmbH) *Thiazolidine derivs. for the treatment and prevention of metabolic bone disorders.* WO 0018746.

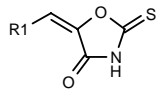
288286

5-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-2-thioxo-oxazolidin-4-one



C18 H23 N O3 S; Mol wt: 333.4497

ACTION – Agent with the ability to stimulate parathyroid hormone (PTH) receptor-mediated adenylate cyclase (cAMP) formation, potentially useful for the treatment and prevention of metabolic bone disorders, particularly for the local or systemic treatment of osteoporosis, rheumatoid arthritis, osteoarthritis and degenerative arthrosis. Other exemplified oxazolidine derivatives are:



Compound	R1	Formula
288287	9-phenanthrenyl	C ₁₈ H ₁₁ NO ₂ S
288288	2-benzofuryl-CH=CH	C ₁₄ H ₉ NO ₃ S
288289	2-benzothieryl-CH=CHCH=CH	C ₁₆ H ₁₁ NO ₂ S ₂
288290	4-Ph-Ph	C ₁₆ H ₁₁ NO ₂ S
288292	3-(C6H13O)-Ph	C ₁₆ H ₁₉ NO ₃ S
288293	4-C5H11-Ph	C ₁₅ H ₁₇ NO ₂ S

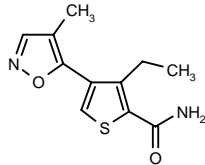
SOURCE – Roche Diagnostics.

REFERENCES

1. Esswein, A. et al. (Roche Diagnostics GmbH) *Oxazolidine derivs. for the treatment and prevention of metabolic bone disorders*. WO 0018745.

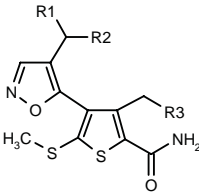
288405

3-Ethyl-4-(4-methylisoxazol-5-yl)thiophene-2-carbox-amide



C11 H12 N2 O2 S; Mol wt: 236.2938

ACTION – Agent for the treatment or prevention of bone or nerve disorders that acts by potentiating the functions of cell differentiation-inducing factors. Compound was shown to increase alkaline phosphatase, as well as to stimulate nodule induction in rat fetal parietal bone osteoblast cultures at a concentration of 2.5 µg/ml. A representative compound from a series of substituted isoxazolythiophene derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
288406	H	H	H	C ₁₁ H ₁₂ N ₂ O ₂ S ₂
288407	H	H	Me	C ₁₂ H ₁₄ N ₂ O ₂ S ₂
288408	Me	Me	H	C ₁₃ H ₁₆ N ₂ O ₂ S ₂

SOURCE – Taisho.

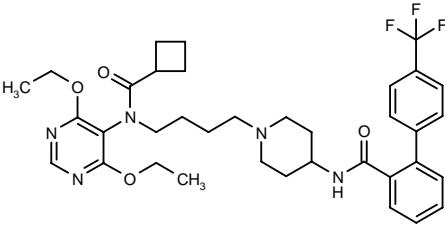
REFERENCES

1. Harada, M. et al. (Taisho Pharmaceutical Co., Ltd.) *Substd. isoxazolythiophene cpds*. WO 0018765.

TREATMENT OF LIPOPROTEIN DISORDERS

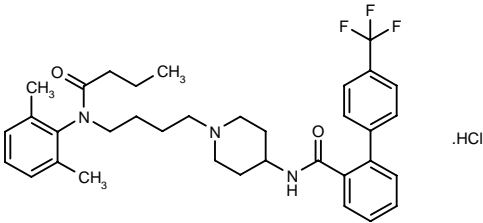
287730

N-[1-[4-[*N*-(Cyclobutylcarbonyl)-*N*-(4,6-diethoxypyrimidin-5-yl)amino]butyl]piperidin-4-yl]-4'-(trifluoromethyl)biphen-yl-2-carboxamide



C36 H44 F3 N5 O4; Mol wt: 667.7686

ACTION – An inhibitor of microsomal triglyceride transfer protein (MTP) proven to inhibit apolipoprotein B (apoB) secretion in HepG2 cells (IC₅₀ = 1.6 nM), potentially useful for the treatment of lipoprotein disorders. Another related compound is:



287731: C35 H42 F3 N3 O2 . HCl

SOURCE – Wakunaga.

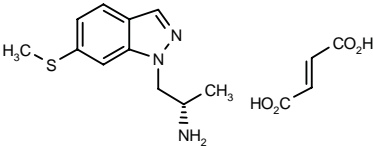
REFERENCES

1. Yokomoto, M. et al. *Development of novel MTP inhibitors having an anilide structure*. 120th Annu Meet Pharm Soc Jpn (March 29-31, Gifu) 2000, Abst 30-PB-12-36.

TREATMENT OF OBESITY
AND NUTRITIONAL DISORDERS

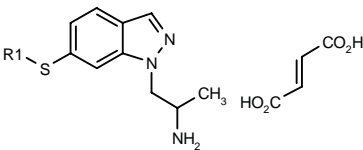
287939

1-[6-(Methylsulfanyl)-1*H*-indazol-1-yl]propan-2(*S*)-amine fumarate



C11 H15 N3 S . C4 H4 O4; Mol wt: 337.3981

ACTION – Selective, direct-acting 5-HT_{2C} receptor agonist, particularly useful in the treatment of obesity. It gave respective K_i values of 7 and 3 nM for 5-HT_{2C} and 5-HT_{2B} receptors in binding assays. In a functional assay, it showed EC₅₀ values for human 5-HT_{2A} and 5-HT_{2C} receptors of 12 nM and 1 nM, respectively, and relative efficacies (5-HT = 100%) of 74 and 89%, respectively. The compound induced a specific 5-HT_{2C} syndrome in rats, maintaining significant pharmacological activity for at least 180 min after an s.c. dose of 1 mg/kg, and regulated feeding behavior in food-deprived animals with significant hypophagia 4 h after the same dose. The compound may also be useful in the treatment of CNS disorders, damage to the CNS, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus and sleep apnea. Other exemplified indazole derivatives are:



Compound	R1	Isomer	Formula
287940	Me		C ₁₁ H ₁₅ N ₃ S.C ₄ H ₄ O ₄
287941	Me	R	C ₁₁ H ₁₅ N ₃ S.C ₄ H ₄ O ₄
287942	Ph	S	C ₁₆ H ₁₇ N ₃ S.C ₄ H ₄ O ₄

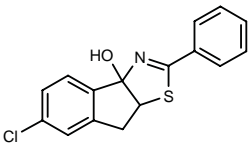
SOURCE – Vernalis Research.

REFERENCES

1. Adams, D.R. et al. (Vernalis Research Ltd.) *Chemical cpds. VIII*. WO 0017170.

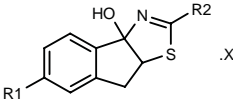
288210

6-Chloro-2-phenyl-8,8a-dihydro-3a*H*-indeno[1,2-*d*]thiazol-3a-ol



C16 H12 Cl N O S; Mol wt: 301.7958

ACTION – Agent for the treatment or prevention of obesity and type 2 diabetes proven to decrease condensed milk consumption by 95% in fasted mice pretreated with 50 mg/kg p.o. Other compounds from this series of indeno-, naphtho- and benzocyclohepta-dihydrothiazole derivatives include the following:



Compound	R1	R2	X	Formula
288211	3-CF3-Ph	Me	HBr	C ₁₈ H ₁₄ F ₃ NOS.HBr
288213	Cl	Ph	HCl	C ₁₆ H ₁₂ ClNOS.HCl
288214	Cl	2,4-(Cl)2-Ph	HBr	C ₁₆ H ₁₀ Cl ₃ NOS.HBr
288215	Cl	Et	HBr	C ₁₂ H ₁₂ ClNOS.HBr
288216	Cl	4-Pyr		C ₁₅ H ₁₁ ClN ₂ OS
288217	Cl	4-Cl-Ph		C ₁₆ H ₁₁ Cl ₂ NOS

SOURCE – Aventis Pharma.

REFERENCES

1. Jähne, G. et al. (Aventis Pharma Deutschland GmbH) *Indeno-, naphto- and benzocyclohepta dihydrothiazole derivs., the production thereof and their use as anorectic medicaments*. DE 19844547, WO 0018749.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

LERIDISTIM

Prop INN; USAN

275783

14-L-Alanine-50-L-aspartic acid-14-125-interleukin 3 (human reduced) fusion protein with 17-L-serine-granulocyte colony stimulating factor (human reduced)

SC-70935

ACTION – Genetically engineered multifunctional hematopoietic agent, a dual receptor agonist for the human IL-3 and G-CSF receptor complexes proven to induce cell proliferation in AML-139 (IL-3- and CSF-responsive), TF-1 (IL-3-responsive) and BaF3/G-CSFR (G-CSF-responsive) cell lines (IC₅₀ = 2.8, 27.8 and 11.8 pM, respectively). Compound showed nanomolar affinity for both IL-3α and IL-3α/β receptors (IC₅₀ = 61 and 15 nM, respectively) and inhibited [¹²⁵I]-G-CSF binding in BaF3/G-CSFR cells with an IC₅₀ value of 1 nM. In a nonhuman primate model of radiation-induced myelo-suppression, compound induced a dramatic hematopoietic recovery with significant improvement in neutrophil and platelet nadirs, as well as a reduction in the duration of neutropenia and thrombocytopenia. Phase I/II clinical studies in patients with relapsed lymphoma receiving ESHAP (etoposide, cisplatin, methylprednisolone and ara-C) demonstrated that compound is safe, well tolerated and effective as a hematopoietic agent.

SOURCES – Pharmacia; Yamanouchi.

REFERENCES

1. Blalock, W.L. et al. *Signal transduction, cell cycle regulatory, and anti-apoptotic pathways regulated by IL-3 in hematopoietic cells: Possible sites for intervention with anti-neoplastic drugs.* Leukemia 1999, 13(8): 1109.

2. Haylock, D.N. et al. *Combinations of chimeric receptor agonists provide potent stimulation of CD34+ cells.* 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 2487.

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8. *Monsanto: Q4 and year-end 1998 highlights.* DailyDrugNews.com (Daily Essentials) 1999, Jan 25.

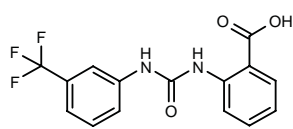
9. *Proposed international nonproprietary names (Prop. INN): List 80.* WHO Drug Inf 1998, 12(4): 266.

10. *Yamanouchi exercises option to license three Searle compounds.* DailyDrugNews.com (Daily Essentials) 2000, March 9.

NS-1652*

259892

2-[3-[3-(Trifluoromethyl)phenyl]ureido]benzoic acid



C15 H11 F3 N2 O3; Mol wt: 324.2569

ACTION – Agent for the treatment of sickle cell anemia, an inhibitor of anion conductance shown to selectively decrease chloride conductance in normal red blood cells (IC₅₀ = 0.62 μM), as well as in oxygenated and deoxygenated sickle cells. *Ex vivo* experiments demonstrated that compound (given i.v. at 50 mg/kg) was able to block by 90% chloride conductance induced by valinomycin in murine erythrocytes. It was well tolerated in mice and rats and had no behavioral or cardiovascular effects.

SOURCE – NeuroSearch.

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3. Bennekou, P. et al. *Volume control in sickle cells is facilitated by the novel anion conductance inhibitor NS1652.* Blood 2000, 95(5): 1842.

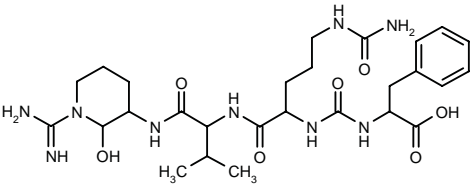
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DENTAL AGENTS

FA-70C1

288539

N-[N-[1-[N-[1-[N-(1-Amidino-2-hydroxypiperidin-3-yl)-carbamoyl]-2-methylpropyl]carbamoyl]-4-ureidobutyl]-carbamoyl]-DL-phenylalanine



C27 H43 N9 O7; Mol wt: 605.6927

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SOURCE – Taisho.

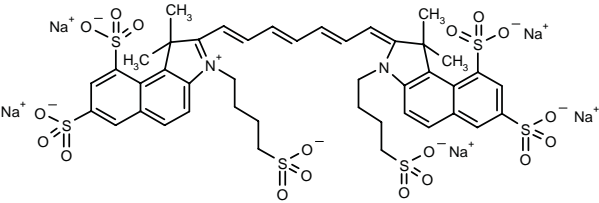
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1. Kitano, S. et al. (Taiho Pharmaceutical Co., Ltd.) *FA-70C1 substances.* JP 2000072797.

DIAGNOSTIC AGENTS

288084

4-[2-[7-[1,1-Dimethyl-7,9-disulfo-3-(4-sulfobutyl)-2,3-dihydro-1H-benzo[e]indol-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-7,9-disulfo-1H-benzo[e]indolium-3-yl]-1-butanedisulfonate pentasodium salt



C43 H43 N2 Na5 O18 S6; Mol wt: 1183.1550

SOURCES – Pharmacia; Yamanouchi.

REFERENCES

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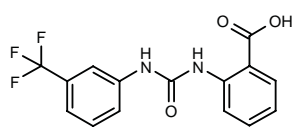
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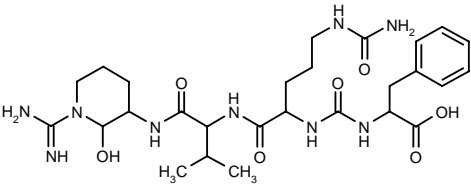
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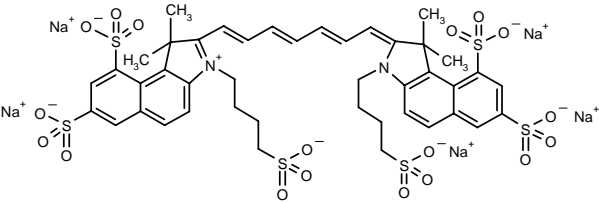
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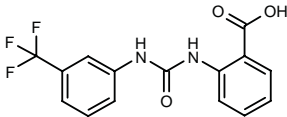
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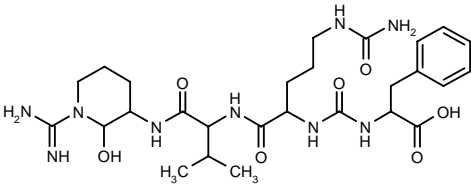
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SOURCE – Taisho.

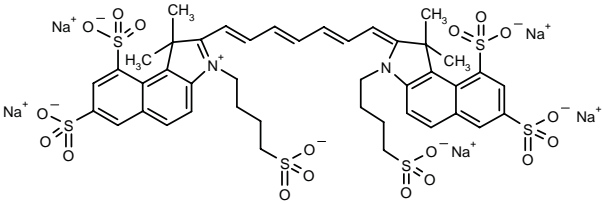
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C43 H43 N2 Na5 O18 S6; Mol wt: 1183.1550

ACTION – Fluorescent contrast agent with high solubility in water and low toxicity that emits fluorescence in the near infrared region, passing through living tissues. Potentially useful in tumor imaging and angiography. The compound showed a partition coefficient (log Po/w in butanol/water) of –2.00 or less and an LD₅₀ value above 1010 mg/kg i.v. in mice. In experimental fluorescence imaging tests in mice bearing colon carcinoma, this compound generated clearer images of tumor and remained in plasma longer than previously known compounds. It also showed a good profile when tested for blood vessel imaging in nude mice.

SOURCES – Fuji Photo Film; Schering AG.

REFERENCES

1. Miwa, N. et al. (Schering AG;Fuji Photo Film Co., Ltd.) *Near infrared fluorescent contrast agent and fluorescence imaging.* WO 0016810.

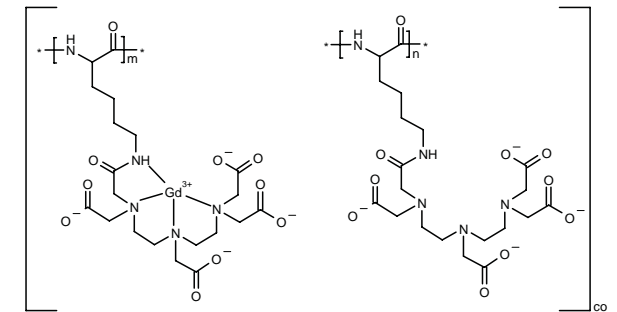
288106

Polyion complex of PLL(Gd-DTPA)(16%) and PDEAMA in a charge ratio of 1:1

PLL(Gd-DTPA)(16%)

288107

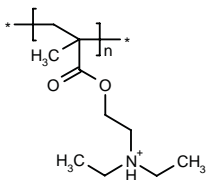
Copolymer of poly-L-lysine (PLL) and diethylenetriamine-pentacetic acid (DTPA) wherein Gd has been introduced into 16% of the DTPA moiety, with an average molecular weight of 50,000



PDEAMA

288108

Poly[2-(diethylamino)ethyl methacrylate] with an average molecular weight of 86,000



ACTION – Magnetic resonance imaging (MRI) contrast agent comprising a complex of a polyanionic gadolinium (Gd)-type contrast agent and a cationic polymer and which expresses an MRI capability at neutral pH in the presence of a polymer electrolyte, but shows no imaging capability in its absence due to its balance between positive and negative charges; since specific polymer electrolytes are expressed on the surface of abnormal cells such as tumor cells, this allows images only of tumor or specific organs, thus improving the detection sensitivity of the contrast agent. Compound provided selective imaging of tumors as compared to normal muscle tissue when injected into mice bearing colon 26 adenocarcinomas. LD₅₀ = 459 mg/kg i.v. in mice.

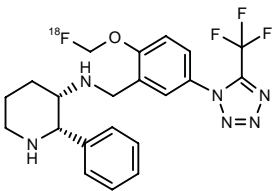
SOURCE – Schering AG.

REFERENCES

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288341

N-[2-([¹⁸F]-Fluoromethoxy)-5-[5-(trifluoromethyl)-1*H*-tetrazol-1-yl]benzyl]-*N*-[2(*S*)-phenylpiperidin-3(*S*)-yl]-amine



C21 H22 F4 N6 O; Mol wt: 449.4398

ACTION – Radiolabeled tachykinin NK₁ receptor antagonist useful for labeling and diagnostic imaging of NK₁ receptors, especially for positron emission tomographic (PET) imaging of NK₁ receptors in the brain, as research or clinical tools.

SOURCE – Merck & Co.

REFERENCES

1. Burns, H.D. et al. (Merck & Co., Inc.) *Radiolabeled neurokinin-1 receptor antagonists.* WO 0018403.

JLP5B9

286961

IgM monoclonal antibody against capsular polysaccharides of Neisseria meningitidis B that bears polysialic acid groups, and that recognizes embryonic neural cell adhesion molecule (eNCAM) and is specifically directed against polysialic acid moieties of NCAM

ACTION – Tumor marker, a monoclonal antibody of the IgM type directed against capsular polysaccharides of *Neisseria meningitidis* B that recognizes neuroendocrine markers commonly found on small cell lung cancer such as neural cell adhesion molecule (NCAM) and the embryonic NCAM (eNCAM). Potentially useful as a specific probe for the detection of eNCAM in lung tumor tissue and in sera from lung cancer patients.

SOURCES – CNRS; University of Pittsburgh, Pittsburgh, PA (US).

REFERENCES

1. Del Rio, M. et al. *JLP5B9: New monoclonal antibody against polysialylated neural cell adhesion molecule is of value in phenotyping lung cancer*. J Immunol Methods 2000, 233(1-2): 21.

LEUTECH™

253959

99m-Tc-labeled anti-CD15 IgM murine monoclonal antibody

ACTION – Neutrophil-specific ^{99m}Tc-labeled anti-CD15 monoclonal antibody for diagnosing equivocal appendicitis. Compound enables the rapid and safe imaging of acute appendicitis, is injected intravenously and accumulates quickly at the site of infection to gave a clear image of inflamed appendix on a γ camera. Currently under FDA review for this indication. Clinical trials are planned to demonstrate the safety and efficacy of compound in the diagnosis of other types of infections including osteomyelitis and several additional soft tissue infections.

SOURCES – Mallinckrodt; Palatin Technologies.

REFERENCES

1. Kipper, S.L. et al. *Neutrophil-specific Tc-99m-labeled anti-CD15 monoclonal antibody imaging for diagnosis of equivocal appendicitis*. J Nucl Med 2000, 41(3): 449.

2. Rypins, E.B. and Kipper, S.L. *A new 99m-Tc-labelled antibody (LeuTech) for diagnosing acute appendicitis with equivocal presentation*. Dig Dis Week (May 16-19, Orlando) 1999, Abst 2180.

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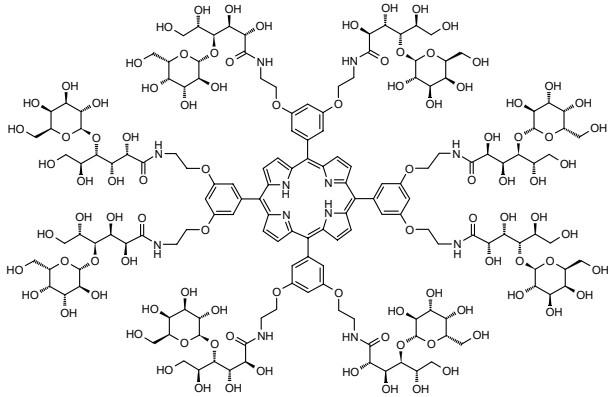
16. *Palatin to meet with FDA to discuss LeuTech in late July*. DailyDrugNews.com (Daily Essentials) 1998, May 14.

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DRUG DELIVERY

286861

5,10,15,20-Tetrakis[3,5-bis[2-[4-O-(β-L-galactopyranosyl)-L-gluconamido]ethoxy]phenyl]porphyrin



C156 H230 N12 O96; Mol wt: 3809.5210

ACTION – Highly saccharide-functionalized porphyrin with masked hydrophobicity for saccharide-directed cell recognition and molecular delivery, proven to be captured by hepatocytes.

SOURCES – Japan Science and Technology Corporation (JST); Kyushu University, Fukuoka (JP).

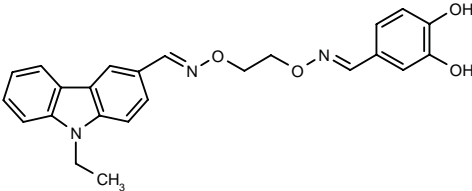
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PHARMACOLOGICAL TOOLS

286500

9-Ethyl-9H-carbazole-3-carbaldehyde O-[2-[(E)-(3,4-dihydroxybenzylidene)aminooxy]ethyl]oxime



C24 H23 N3 O4; Mol wt: 417.4627

ACTION – Potent subtype-selective tyrosine kinase c-Scr inhibitor (IC₅₀ = 64 nM) with > 75-fold selectivity over Lyn and Fyn tyrosine kinase and over 1,000-fold selectivity over Lck kinase. Potentially useful as a pharmacological tool for elucidating the pathophysiological role of this tyrosine kinase.

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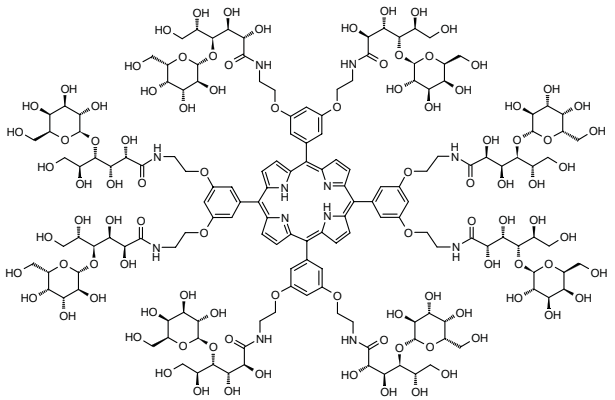
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286861

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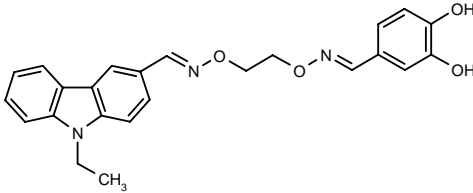
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PHARMACOLOGICAL TOOLS

286500

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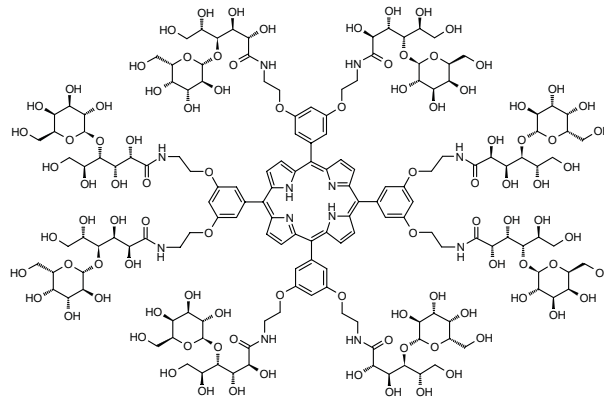
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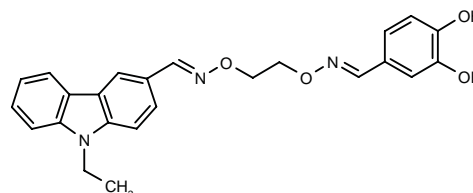
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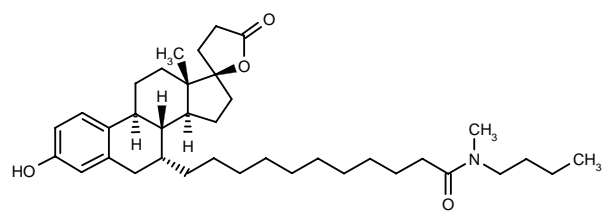
SOURCES – University of California, Berkeley, Berkeley, CA (US); University of Pennsylvania, Philadelphia, PA (US).

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1. Dustin, J. et al. *Combinatorial target-guided ligand assembly: Identification of potent subtype-selective c-Src inhibitors*. Proc Natl Acad Sci USA 2000, 97(6): 2419.

287254

7α-[10-(*N*-Butyl-*N*-methylcarbamoyl)decyl]-3-hydroxy-19-nor-17α-pregna-1,3,5(10)-triene-21,17-carbolactone



C37 H57 N O4; Mol wt: 579.8603

Colorless oil.

ACTION – 17β-Hydroxysteroid dehydrogenase (17β-HSD) type 2 inhibitor (IC₅₀ = 0.35 μM in microsomal fraction of human placenta) with selectivity over type 1 17β-HSD. In estrogen-sensitive (ER+) human breast cancer ZR-75-1 cells, compound showed antiestrogenic activity at higher concentrations (1 μM), reversing the estrogenic effect of estradiol (0.1 nM) by 87%, but it had no proliferation-stimulating effect (estrogenic effect) at these concentrations. No androgenic effects were seen in androgen-sensitive (AR+) human cancer Shionogi cells at up to 1 μM. Potentially useful as a pharmacological tool to elucidate the physiological role of this isoform of the enzyme.

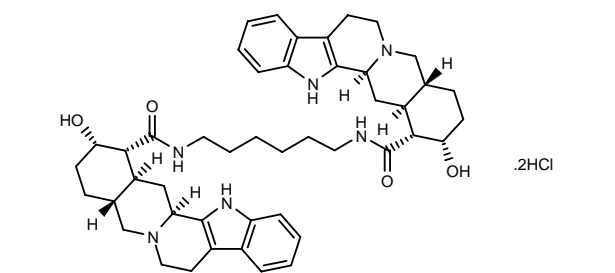
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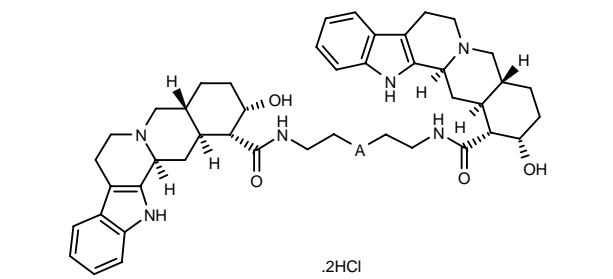
288481

N,N'-Bis[(1*R*,2*S*,4*aR*,13*bS*,14*aS*)-2-hydroxy-1,2,3,4,4*a*,5,7,8,13*b*,14,14*a*-dodecahydrobenz[*g*]indolo[2,3-*a*]quinolizin-1-ylcarbonyl]hexane-1,6-diamine dihydrochloride



C46 H60 N6 O4 . 2HCl; Mol wt: 833.9398

ACTION – High-affinity α_{2A}-adrenoceptor ligand (K_i = 1.35 nM) with more than 100-fold selectivity over α_{2B}-adrenoceptors (K_i = 166.2 nM). A potentially valuable pharmacological tool for studying the pathophysiological significance of α_{2A}-adrenoceptors. Other representative yohimbine dimers are:



Compound	R1	Formula
288480	-CH2-	C ₄₅ H ₆₀ Cl ₂ N ₆ O ₄
288482	-(CH2)4-	C ₄₈ H ₆₆ Cl ₂ N ₆ O ₄
288483	-(CH2)6-	C ₅₀ H ₇₀ Cl ₂ N ₆ O ₄

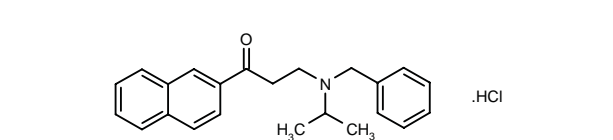
SOURCES – University of Mississippi, Oxford, MS (US); University of Tennessee, Memphis, Memphis, TN (US).

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1. Zheng, W. et al. *Yohimbine dimers exhibiting binding selectivities for human α_{2a} - versus α_{2b} adrenergic receptors*. Bioorg Med Chem Lett 2000, 10(7): 627.

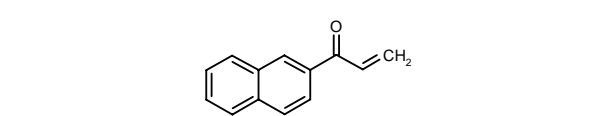
288629

3-(*N*-Benzyl-*N*-isopropylamino)-1-(2-naphthyl)propan-1-one hydrochloride



C23 H25 N O . HCl; Mol wt: 367.9174

ACTION – Potent inhibitor of the tyrosine kinase Janus kinase 3 (Jak3; pIC₅₀ = 7.1) with high selectivity relative to Jak1 and epidermal growth factor (EGF) receptor tyrosine kinase (pIC₅₀ = 4.4 and 5.6, respectively). Potentially useful as a pharmacological tool for further investigations of the role of Jak3. The breakdown product of title compound showed a similar profile:



288630: C13 H10 O

SOURCE – AstraZeneca.

REFERENCES

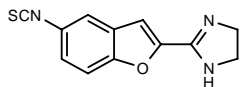
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BU-99006

288635

2-(5-Isothiocyanato-1-benzofuran-2-yl)-4,5-dihydro-1*H*-imidazole

N-[2-(4,5-Dihydro-1*H*-imidazol-2-yl)-1-benzofuran-5-yl]-isothiocyanate



C₁₂ H₉ N₃ O S; Mol wt: 243.2891

ACTION – Potent, selective and irreversible ligand for the imidazoline I₂ binding site ($K_i = 2.3$ nM for I₂; $IC_{50} = 8100$ nM for I₁; $K_i = 16,300$ nM for α_2 -adrenoceptor), potentially useful as a pharmacological tool for elucidating the role of imidazoline binding sites.

SOURCE – University of Bristol, Bristol (GB).

REFERENCES

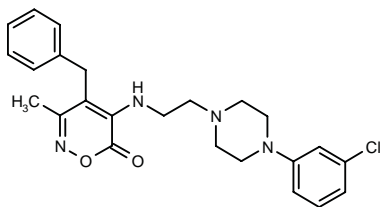
1. Coates, P.A. et al. *Probes for imidazole binding sites: Synthesis and evaluation of a selective, irreversible I₂ ligand*. *Bioorg Med Chem Lett* 2000, 10(6): 605.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

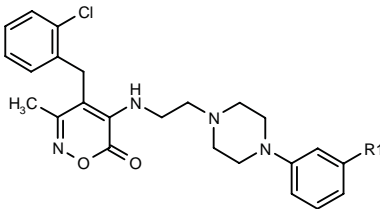
288473

5-[2-[4-(3-Chlorophenyl)piperazin-1-yl]ethylamino]-3-methyl-4-benzyl-6*H*-1,2-oxazin-6-one



C₂₄ H₂₇ Cl N₄ O₂; Mol wt: 438.9563

ACTION – Analgesic agent with significant antinociceptive effect in the phenylbenzoquinone-induced writhing test in mice (ED₅₀ = 19.7 mg/kg i.p.), being more potent than paracetamol (ED₅₀ = 228.6 mg/kg i.p.) and almost as active as trazodone (ED₅₀ = 10.2 mg/kg i.p.). Compound failed to potentiate analgesia induced by morphine and its analgesic effect seems to be mediated by mu-opioid and noradrenergic mechanisms, as demonstrated by the ability of naloxone and yohimbine to reverse the analgesic effect of the compound. No behavioral, neurological or autonomic effects were seen. Other oxazinones are:



Compound	R1	Formula
288474	H	C ₂₄ H ₂₇ ClN ₄ O ₂
288475	Cl	C ₂₄ H ₂₆ Cl ₂ N ₄ O ₂

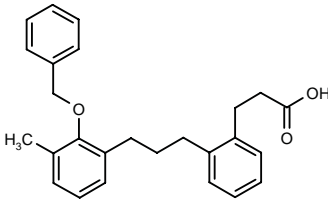
SOURCE – Université d’Auvergne-Clermont-Ferrand, Clermont-Ferrand (FR).

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1. Bebot, M. et al. *Synthesis and analgesic effects of 5-[4-(aryl)piperazin-1-yl]alkylamino]-4-benzyl-3-methyl-1,2-oxazin-6-ones*. *Arzneim-Forsch Drug Res* 2000, 50(4): 353.

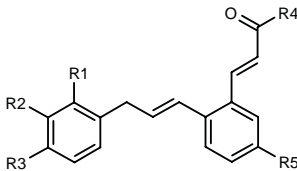
288598

3-[2-[3-(2-Benzoyloxy-3-methylphenyl)propyl]phenyl]-propionic acid

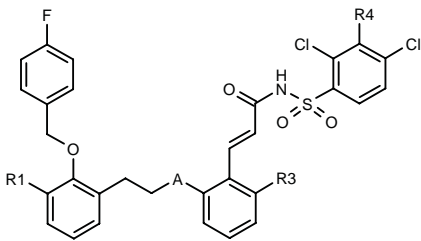


C₂₆ H₂₈ O₃; Mol wt: 388.5042

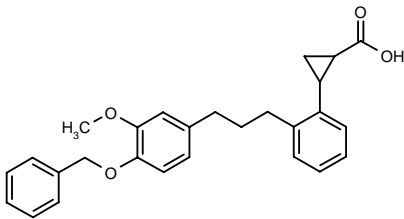
ACTION – Prostaglandin E (PGE), or EP, receptor ligand with analgesic, antipyretic and antiinflammatory properties and reduced adverse effects such as gastrointestinal or renal toxicity. It is also reported to be useful for the treatment of other PGE-mediated disorders. Other exemplified compounds include the following:



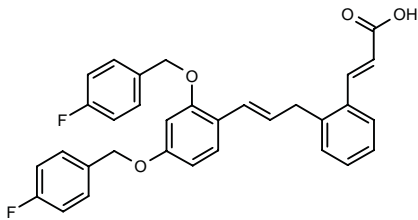
Compound	R1	R2	R3	R4	R5	Formula
288600	H	OMe	OMe	OH	H	C ₂₀ H ₂₀ O ₄
288601	2,6-(Cl)2-Ph-CH ₂ O	Me	H	OH	H	C ₂₆ H ₂₂ Cl ₂ O ₃
288602	-OCH=C(Ph)-	H	H	ONa	H	C ₂₆ H ₁₉ NaO ₃
288605	4-F-PhCH ₂ O	H	H	2-Cl-6-Me-Ph-SO ₂ NH	F	C ₃₂ H ₂₆ ClF ₂ NO ₄ S



Compound	R1	R2	R3	R4	A	Formula
288603	Me	2,3,4-(Cl)3-Ph-SO2NHCOCH=CH	F	Cl	S	C ₃₁ H ₂₄ Cl ₃ F ₂ NO ₄ S ₂
288604	OMe	2,4-(Cl)2-Ph-SO2NHCOCH=CH	H	H	O	C ₃₁ H ₂₆ Cl ₂ FNO ₆ S



288599: C27 H28 O4



288606: C32 H26 F2 O4

SOURCE – Merck Frosst.

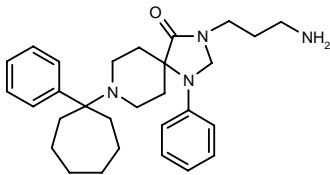
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289070

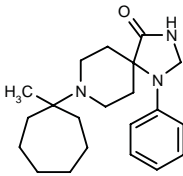
3-(3-Aminopropyl)-1-phenyl-8-(1-phenylcycloheptyl)-1,3,8-triazaspiro[4.5]decan-4-one

1-(3-Aminopropyl)-3-phenyl-1'-(1-phenylcycloheptyl)-spiro[imidazolidine-4,4'-piperidin]-5-one



C29 H40 N4 O; Mol wt: 460.6620

ACTION – ORL1 (N/OFQ) receptor agonist with higher affinity for ORL1 receptors than for mu-receptors in HEK293 and CHO-K1 cell membranes transfected with human ORL1 and mu-receptors, respectively. Particularly useful as an analgesic, diuretic, anesthetic and antiinflammatory agent. Another specifically claimed 1,3,8-triazaspiro[4,5]decanone compound is:



289071: C21 H31 N3 O

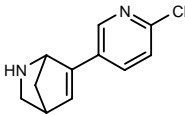
SOURCE – Pfizer.

REFERENCES

1. Ito, F. and Ohashi, Y. (Pfizer Inc.) *1,3,8-Triazaspiro[4,5]decanone cpds. as orl1-receptor agonists*. EP 0997464, JP 2000128879.

289277

6-(6-Chloropyridin-3-yl)-2-azabicyclo[2.2.1]hept-5-ene



C11 H11 Cl N2; Mol wt: 206.6749

ACTION – Epibatidine analogue, a potent nonopioid analgesic with nicotinic acetylcholine receptor-agonist activity. In a competitive assay against [³H]-epibatidine in rat brain P2 membranes, it gave a K_i value of 0.26 nM compared with 0.036 nM for epibatidine.

SOURCE – Isis Innovation.

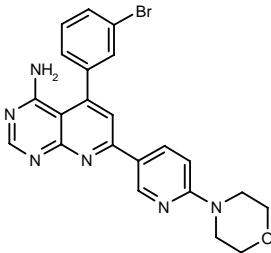
REFERENCES

1. Hodgson, D.M. and Maxwell, C.R. (Isis Innovation, Ltd.) *Epibatidine analogues as acetylcholine receptor antagonists*. WO 0023424.

289331

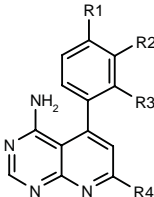
5-(3-Bromophenyl)-7-[6-(4-morpholinyl)pyridin-3-yl]-pyrido[2,3-*d*]pyrimidin-4-amine

5-(3-Bromophenyl)-7-[6-(4-morpholinyl)pyridin-3-yl]-pyrido[2,3-*d*]pyrimidin-4-ylamine



C22 H19 Br N6 O; Mol wt: 463.3371

ACTION – Adenosine kinase inhibitor (IC_{50} = 1 nM) proven active *in vivo* in the carrageenan-induced hyperalgesia test in rats, with an ED_{50} of 0.6 μ mol/kg i.p. It is expected to be useful for the treatment of cerebral and myocardial ischemia, neurological disorders, nociperception, inflammation, immunosuppression, gastrointestinal disorders, diabetes and sepsis. Other exemplified compounds from this series of 5,7-disubstituted-4-aminopyrido[2,3-*d*]pyrimidine derivatives are:



Compound	R1	R2	R3	R4	Formula
289332	H	Br	H	6-[2(S)-(MeOCH2)-1-pyrrolidinyl]-3-Pyr	C ₂₄ H ₂₃ BrN ₆ O
289333	H	Br	H	6-[2(S)-(CH2CH2OH)-1-pyrrolidinyl]-3-Pyr	C ₂₄ H ₂₃ BrN ₆ O
289334	H	H	Br	6-(4-OH-1-Pip)-3-Pyr	C ₂₃ H ₂₁ BrN ₆ O
289335	F	H	H	6-(1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)-3-Pyr	C ₂₅ H ₂₃ FN ₆ O ₂
289336	H	H	Br	6-(4-OH-1-Pip)-3-pyridazinyl	C ₂₂ H ₂₀ BrN ₇ O
289337	H	Br	H	6-(1,4-dioxo-8-azaspiro-[4.5]dec-8-yl)-3-pyridazinyl	C ₂₄ H ₂₂ BrN ₇ O ₂
289339	H	Br	H	2-(4-morpholinyl)-5-thiazolyl	C ₂₀ H ₁₇ BrN ₆ OS
289342	H	Br	H	6-[4-(EtON=)-1-Pip]-3-Pyr	C ₂₅ H ₂₄ BrN ₇ O
289343	H	Br	H	5-(1,4-dioxo-8-azaspiro-[4.5]dec-8-yl)-2-pyrazinyl	C ₂₄ H ₂₂ BrN ₇ O ₂

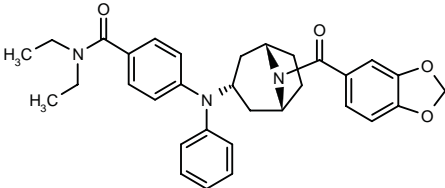
SOURCE – Abbott.

REFERENCES

1. Bhagwat, S.S. et al. (Abbott Laboratories Inc.) *5,7-Disubstd.-4-aminopyrido[2,3-d]pyrimidine cpds.* WO 0023444.

289883

4-[*N*-(8-(1,3-Benzodioxol-5-ylcarbonyl)-8-azabicyclo[3.2.1]oct-3-*endo*-yl)]-*N*-phenylamino]-*N,N*-diethylbenzamide



C32 H35 N3 O4; Mol wt: 525.6455

ACTION – Potent delta-opioid (DOP, OP_1) receptor agonist, a 4-diarylaminotropane with high affinity for this receptor (K_i = 0.2 nM) and selectivity over the mu-opioid receptor (MOP, OP_3 ; K_i = 172 nM). Potentially useful as an analgesic agent.

SOURCE – R.W. Johnson.

REFERENCES

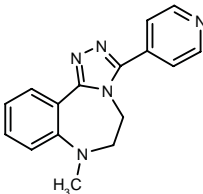
1. Boyd, R.E. et al. *Synthesis and binding affinities of 4-diarylaminotropanes, a new class of delta opioid agonists.* Bioorg Med Chem Lett 2000, 10(10): 1109.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

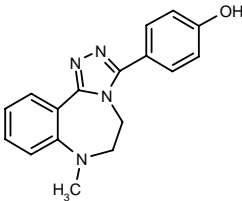
288470

7-Methyl-3-(4-pyridyl)-6,7-dihydro-5 *H*-[1,2,4]triazolo[4,3-*d*][1,4]benzodiazepine

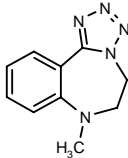


C16 H15 N5; Mol wt: 277.3295

ACTION – Tricyclic 1,4-benzodiazepine with CNS depressant activity and a pharmacological profile similar to that of chlordiazepoxide. In mice, compound exhibited a hypnotic effect, myorelaxant effect, anticonvulsant activity against pentylenetetrazol-induced seizures (ED_{50} = 83.7 mg/kg p.o.) and strong anxiolytic activity. It showed low toxicity, with an LD_{50} value > 400 mg/kg p.o. in mice. Other representative compounds within this series of triazolo[4,3-*d*] and tetrazolo[1,5-*a*][1,4]benzodiazepines are:



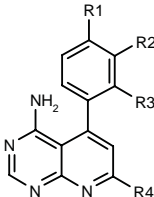
288471: C17 H16 N4 O



288472: C10 H11 N5

SOURCES – CSIC, Madrid (ES); Universidad de La Laguna, La Laguna (ES).

ACTION – Adenosine kinase inhibitor (IC_{50} = 1 nM) proven active *in vivo* in the carrageenan-induced hyperalgesia test in rats, with an ED_{50} of 0.6 μ mol/kg i.p. It is expected to be useful for the treatment of cerebral and myocardial ischemia, neurological disorders, nociperception, inflammation, immunosuppression, gastrointestinal disorders, diabetes and sepsis. Other exemplified compounds from this series of 5,7-disubstituted-4-aminopyrido[2,3-*d*]pyrimidine derivatives are:



Compound	R1	R2	R3	R4	Formula
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289334	H	H	Br	6-(4-OH-1-Pip)-3-Pyr	C ₂₃ H ₂₁ BrN ₆ O
289335	F	H	H	6-(1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)-3-Pyr	C ₂₅ H ₂₃ FN ₆ O ₂
289336	H	H	Br	6-(4-OH-1-Pip)-3-pyridazinyl	C ₂₂ H ₂₀ BrN ₇ O
289337	H	Br	H	6-(1,4-dioxo-8-azaspiro-[4.5]dec-8-yl)-3-pyridazinyl	C ₂₄ H ₂₂ BrN ₇ O ₂
289339	H	Br	H	2-(4-morpholinyl)-5-thiazolyl	C ₂₀ H ₁₇ BrN ₆ OS
289342	H	Br	H	6-[4-(EtON=)-1-Pip]-3-Pyr	C ₂₅ H ₂₄ BrN ₇ O
289343	H	Br	H	5-(1,4-dioxo-8-azaspiro-[4.5]dec-8-yl)-2-pyrazinyl	C ₂₄ H ₂₂ BrN ₇ O ₂

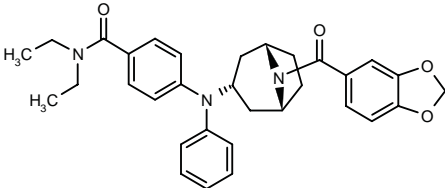
SOURCE – Abbott.

REFERENCES

1. Bhagwat, S.S. et al. (Abbott Laboratories Inc.) *5,7-Disubstd.-4-aminopyrido[2,3-d]pyrimidine cpds.* WO 0023444.

289883

4-[*N*-(8-(1,3-Benzodioxol-5-ylcarbonyl)-8-azabicyclo[3.2.1]oct-3-*endo*-yl)]-*N*-phenylamino]-*N,N*-diethylbenzamide



C32 H35 N3 O4; Mol wt: 525.6455

ACTION – Potent delta-opioid (DOP, OP_1) receptor agonist, a 4-diarylaminotropane with high affinity for this receptor (K_i = 0.2 nM) and selectivity over the mu-opioid receptor (MOP, OP_3 ; K_i = 172 nM). Potentially useful as an analgesic agent.

SOURCE – R.W. Johnson.

REFERENCES

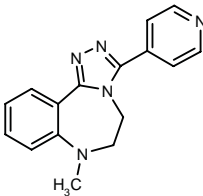
1. Boyd, R.E. et al. *Synthesis and binding affinities of 4-diarylaminotropanes, a new class of delta opioid agonists.* Bioorg Med Chem Lett 2000, 10(10): 1109.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

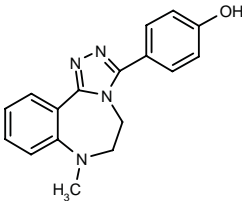
288470

7-Methyl-3-(4-pyridyl)-6,7-dihydro-5 *H*-[1,2,4]triazolo[4,3-*d*][1,4]benzodiazepine

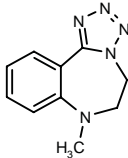


C16 H15 N5; Mol wt: 277.3295

ACTION – Tricyclic 1,4-benzodiazepine with CNS depressant activity and a pharmacological profile similar to that of chlordiazepoxide. In mice, compound exhibited a hypnotic effect, myorelaxant effect, anticonvulsant activity against pentylenetetrazol-induced seizures (ED_{50} = 83.7 mg/kg p.o.) and strong anxiolytic activity. It showed low toxicity, with an LD_{50} value > 400 mg/kg p.o. in mice. Other representative compounds within this series of triazolo[4,3-*d*] and tetrazolo[1,5-*a*][1,4]benzodiazepines are:



288471: C17 H16 N4 O



288472: C10 H11 N5

SOURCES – CSIC, Madrid (ES); Universidad de La Laguna, La Laguna (ES).

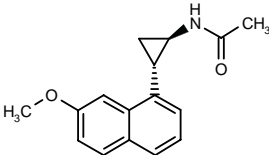
REFERENCES

1. Darias, V. et al. *Pharmacological effects of triazolo[4,3-d] and tetrazolo[1,5-a][1,4]-benzodiazepines on the central nervous system.* *Arzneim-Forsch Drug Res* 2000, 50(4): 323.

2. Madronero, R. and Vega, S. *Synthesis of triazolo[4,3-d]-, tetrazolo[1,5-a]- and quinazolino[3,2-d] [1,4]benzodiazepines.* *J Heterocycl Chem* 1978, 15(7): 1127.

288664

trans-*N*-[2-(7-Methoxynaphthalen-1-yl)cyclopropyl]-acetamide



C16 H17 N O2; Mol wt: 255.3153

ACTION – Agent with high affinity for melatonin receptors, potentially useful in the treatment of disorders involving the melatonergic system such as sleep disorders, anxiety, schizophrenia and depression.

SOURCE – ADIR.

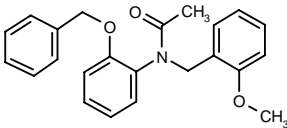
REFERENCES

1. Langlois, M. et al. (ADIR et Cie.) *Cyclic derivs. with a cycloalkylenic chain, process for their preparation and pharmaceutical compsns. containing them.* EP 0994102, FR 2784375, JP 2000136173.

ANXIOLYTICS

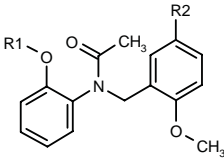
288556

N-(2-Benzoyloxyphenyl)-*N*-(2-methoxybenzyl)acetamide



C23 H23 N O3; Mol wt: 361.4387

ACTION – Agent with high affinity for the MDR (mitochondrial DBI [diazepam binding inhibitor] receptor) site, as demonstrated in binding assays by an IC₅₀ value of 0.72 nM for inhibition of [³H]-PK-11195 binding in rat cerebral cortex mitochondrial preparations. Potentially useful in the treatment of anxiety, depression, epilepsy, sleep and cognition disorders, schizophrenia, motor, eating and circulatory disorders, drug dependence, cancer, lipid metabolism disorders, cerebral infarction, AIDS, Alzheimer’s disease and Huntington’s chorea. Other exemplified compounds from this series of aniline derivatives include the following:



Compound	R1	R2	Formula
288558	3-Pyr-CH2	H	C ₂₂ H ₂₂ N ₂ O ₃
288560	4-Pyr-CH2	H	C ₂₂ H ₂₂ N ₂ O ₃
288561	CH2Ph	OMe	C ₂₄ H ₂₆ NO ₄
288562	4-F-PhCH2	OMe	C ₂₄ H ₂₄ FNO ₄
288564	cyclohexyl	H	C ₂₂ H ₂₇ NO ₃

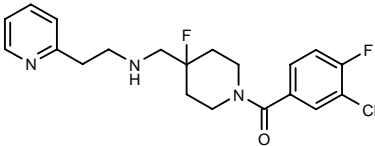
SOURCES – Nihon Nohyaku; Taisho.

REFERENCES

1. Nagamine, M. et al. (Nihon Nohyaku Co., Ltd.;Taisho Pharmaceutical Co., Ltd.) *Aniline derivs.* JP 2000072734.

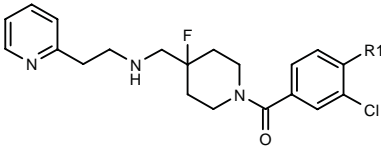
288917

1-(3-Chloro-4-fluorophenyl)-1-[4-fluoro-4-[2-(2-pyridinyl)-ethylaminomethyl]piperidin-1-yl]methanone



C20 H22 Cl F2 N3 O; Mol wt: 393.8628

ACTION – Potent and selective 5-HT_{1A} receptor agonist, as demonstrated *in vitro* by pK_i values of 9.81 and 6.18 for 5-HT_{1A} and dopamine D2 receptors, respectively, being more potent and selective than buspirone (pK_i = 7.65 and 7.49, respectively). Agonist activity was demonstrated *in vivo* in the lower lip retraction assay in rats (ED₅₀ = 0.31 mg/kg p.o. vs. 20 mg/kg p.o. for buspirone). Potentially useful in the treatment of anxiety, pain, depression and neurodegenerative disorders. Other specifically claimed compounds from this series of aryl-[4-fluoro-4-[(2-pyridin-2-yl-ethylamino)methyl]piperidin-1-yl]methanone derivatives are:



Compound	R1	Formula
288918	Cl	C ₂₀ H ₂₂ Cl ₂ FN ₃ O
288919	H	C ₂₀ H ₂₃ ClFN ₃ O

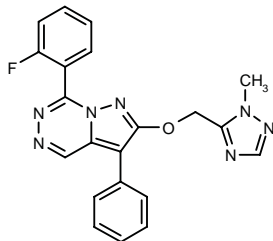
SOURCE – Pierre Fabre.

REFERENCES

1. Vacher, B. et al. (Pierre Fabre Médicament) *Aryl-(4-fluoro-4-[(2-pyridin-2-yl-ethylamino)-methyl]-piperidin-1-yl)-methanone derivs. as 5-HT₁ receptor agonists.* WO 0021953.

289252

7-(2-Fluorophenyl)-2-(1-methyl-1*H*-1,2,4-triazol-5-yl-methoxy)-3-phenylpyrazolo[1,5-*d*][1,2,4]triazine



C21 H16 F N7 O; Mol wt: 401.4034

ACTION – Selective ligand for GABA_A receptors with potential in the treatment of CNS disorders. It has been found to exhibit selective binding affinity for the α2 and/or α3 subunit of the human GABA_A receptor relative to the α1 subunit and is therefore particularly useful for the treatment or prevention of anxiety.

SOURCE – Merck Sharp & Dohme.

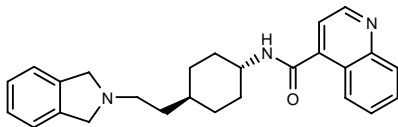
REFERENCES

1. Carling, W.R. et al. (Merck Sharp & Dohme Ltd.) *Pyrazolo-triazine derivs. as ligands for GABA receptors*. WO 0023449.

ANTIPSYCHOTIC DRUGS

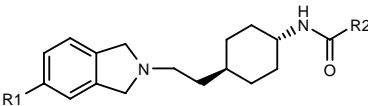
289152

trans-*N*-[4-[2-(2,3-Dihydro-1*H*-isoindol-2-yl)ethyl]cyclohexyl]quinoline-4-carboxamide



C26 H29 N3 O; Mol wt: 399.5351

ACTION – Dopamine D3 receptor modulator for the treatment of psychotic disorders such as schizophrenia. A representative compound from a series of specifically claimed 2,3-dihydro-1*H*-isoindole derivatives, wherein the following are also included:



Compound	R1	R2	Formula
289153	H	3-F-PhCH=CH	C ₂₆ H ₂₉ FN ₂ O
289154	H	2-Naph-CH2	C ₂₈ H ₃₂ N ₂ O
289155	H	4-quinolyl-CH2	C ₂₇ H ₃₁ N ₃ O
289156	CN	4-F-PhCH=CH	C ₂₆ H ₂₈ FN ₃ O
289157	CN	2-MeO-PhCH=CH	C ₂₇ H ₃₁ N ₃ O ₂
289158	CN	3-thienyl-CH=CH	C ₂₄ H ₂₇ N ₃ OS
289159	OSO2Me	4-F-PhCH=CH	C ₂₆ H ₃₁ FN ₂ O ₄ S
289160	OSO2Me	3-(1-pyrazolyl)-Ph	C ₂₇ H ₃₂ N ₄ O ₄ S

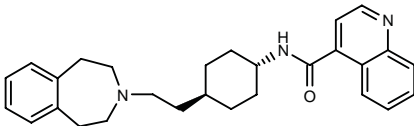
SOURCE – SmithKline Beecham.

REFERENCES

1. Johnson, C.N. and Stemp, G. (SmithKline Beecham plc) *2,3-Dihydro-1H-isoindole derivs. useful as modulators of dopamine D3 receptors (antipsychotic agents)*. WO 0021950.

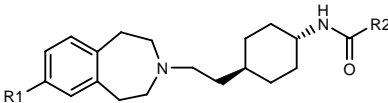
289162

trans-*N*-[4-[2-(2,3,4,5-Tetrahydro-1*H*-3-benzazepin-3-yl)-ethyl]cyclohexyl]quinoline-4-carboxamide



C28 H33 N3 O; Mol wt: 427.5887

ACTION – Dopamine D3 receptor modulator for the treatment of psychotic disorders such as schizophrenia. Other specifically claimed tetrahydrobenzazepines include the following:



Compound	R1	R2	Formula
289165	CN	1H-pyrrolo[2,3- <i>b</i>]pyridin-3-yl	C ₂₇ H ₃₁ N ₅ O
289166	CN	CH2CH2Ph	C ₂₈ H ₃₆ N ₃ O
289167	CN	2-benzofuryl-CH2	C ₂₉ H ₃₃ N ₃ O ₂
289168	Ac	4-F-PhCH2	C ₂₈ H ₃₆ FN ₂ O ₂
289169	Ac	2-NH2-6-benzothiazolyl-CH2	C ₂₉ H ₃₆ N ₄ O ₂ S
289170	3-Me- -1,2,4-oxadiazol-5-yl	2-Naph-CH2	C ₃₃ H ₃₈ N ₄ O ₂
289171	3-Me-5-isoxazolyl	4-F-PhCH=CH	C ₃₁ H ₃₆ FN ₃ O ₂

SOURCE – SmithKline Beecham.

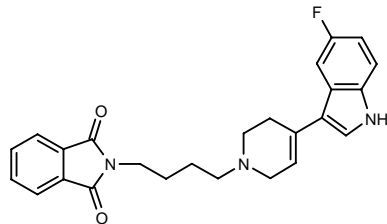
REFERENCES

1. Hadley, M.S. et al. (SmithKline Beecham plc) *Tetrahydrobenzazepine derivs. useful as modulators of dopamine D3 receptors (antipsychotic agents)*. WO 0021951.

289320

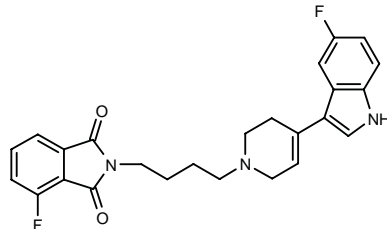
2-[4-[4-(5-Fluoro-1*H*-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]butyl]-2,3-dihydro-1*H*-isoindole-1,3-dione

N-[4-[4-(5-Fluoro-1*H*-indol-3-yl)-1,2,3,6-tetradropyridin-1-yl]butyl]phthalimide



C25 H24 F N3 O2; Mol wt: 417.4816

ACTION – Dual-action antipsychotic agent that antagonizes dopamine D2 receptors and inhibits 5-HT reuptake. The compound is reported to induce less extrapyramidal side effects than available antipsychotic agents. Another exemplified compound from this series of 3-tetrahydropyridin-4-ylindoles is:



289321: C25 H23 F2 N3 O2

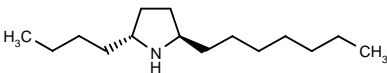
SOURCE – Duphar.

REFERENCES

1. Tulp, M.T.M. et al. (Duphar International Research BV) *3-Tetrahydropyridin-4-yl indoles for treatment of psychotic disorders*. WO 0023441.

289750

2(*R*)-Butyl-5(*R*)-heptylpyrrolidine



C15 H31 N; Mol wt: 225.4169

ACTION – Potent σ -receptor ligand extracted from the culture broth of *Streptomyces longispororuber*. Compound exhibited high affinity and selectivity for σ -receptors, with IC₅₀ values of 2.0 and 22.7 nM, respectively, against σ_1 - and σ_2 -receptors and an IC₅₀ of 40 μ M against dopamine D2 receptors. It did not interact with a number of other receptors including glutamate, muscarinic, nicotinic acetylcholine, 5-HT and GABA receptors at concentrations up to 10 μ M. Potentially useful for the treatment of psychotic disorders including schizophrenia and depression.

SOURCE – Sumitomo Pharmaceuticals.

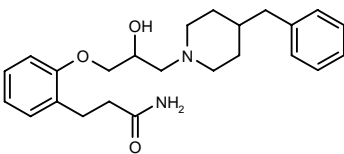
REFERENCES

1. Nakayama, H. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *σ -Receptor-binding inhibitors*. JP 1997295937.
2. Kumagai, K. et al. (2*R-trans*)-2-Butyl-5-heptylpyrrolidine as a potent sigma receptor ligand produced by *Streptomyces longispororuber*. J Antibiot 2000, 53(5): 467.

TREATMENT OF MOOD DISORDERS

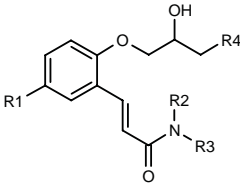
289260

3-[2-[2-Hydroxy-3-(4-benzylpiperidin-1-yl)propoxy]-phenyl]propionamide



C24 H32 N2 O3; Mol wt: 396.5278

ACTION – 5-HT_{1A} receptor ligand with 5-HT reuptake-inhibitory activity, potentially useful as an antidepressant. Other exemplified cinnamic acid amide derivatives and 3-phenylpropionamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
289261	H	H	H	4-Ph-1-Pip	C ₂₃ H ₂₈ N ₂ O ₃
289262	H	-(CH2)4-		4-(4-Me-Ph)-1,2,3,6-tetrahydro-1-Pyr	C ₂₈ H ₃₄ N ₂ O ₃
289265	H	-(CH2)4-		4-(6-MeO-2-Naph)-1,2,3,6-tetrahydro-1-Pyr	C ₃₂ H ₃₆ N ₂ O ₄
289268	H	-CH2CH2OCH2CH2-		4-(3-CF3-Ph)-1,2,3,6-tetrahydro-1-Pyr	C ₂₈ H ₃₁ F ₃ N ₂ O ₄
289270	H	-CH2CH2OCH2CH2-		4-(2-indolyl)-1-Pip	C ₂₉ H ₃₅ N ₃ O ₄
289271	H	-CH2CH2-N(Ac)CH2CH2-		4-(1-Naph)-1-Pip	C ₃₃ H ₃₉ N ₃ O ₄
289272	H	Ph	Me	4-(1-Naph)-1-Pip	C ₃₄ H ₃₆ N ₂ O ₃
289273	H	-CH2CH2OCH2CH2-		4-(2-Naph)-1-Pip	C ₃₁ H ₃₆ N ₂ O ₄
289274	Cl	-CH2CH2OCH2CH2-		4-(2-Naph)-1-Pip	C ₃₁ H ₃₅ ClN ₂ O ₄

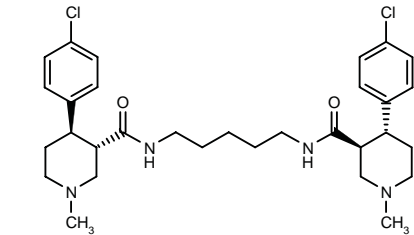
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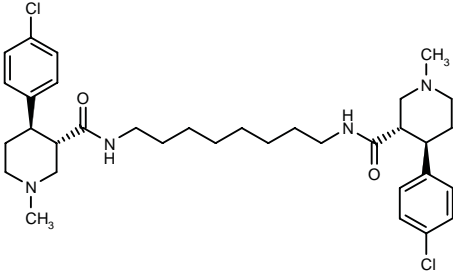
290028^{1,2}

(-)-*trans*-*N,N'*-(1,5-Pentanediy)bis[4-(4-chlorophenyl)-1-methylpiperidine-3-carboxamide]



C31 H42 Cl2 N4 O2; Mol wt: 573.6048

ACTION – Potent and selective 5-HT reuptake inhibitor ($K_i = 1.2$ nM) with more than 1,000-fold selectivity over the dopamine transporter ($K_i = 1960$ nM) and about 300-fold selectivity over the noradrenaline transporter ($K_i = 393$ nM). Potentially useful for the treatment of depression and related psychological disorders. Another related compound is:



290026:² C34 H48 Cl2 N4 O2

SOURCES – Georgetown University, Washington, DC (US); University of Texas Medical Branch at Galveston, Galveston, TX (US).

REFERENCES

1. Kozikowski, A.P. et al. (Georgetown University) *Monomeric and dimeric heterocycles, and therapeutic uses thereof*. WO 0020390.

2. Tamiz, A.P. et al. *Application of the bivalent ligand approach to the design of novel dimeric serotonin reuptake inhibitors*. J Am Chem Soc 2000, 122(22): 5393.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

LEVETIRACETAM

Rec INN

113936

(-)-(S)- α -Ethyl-2-oxo-1-pyrrolidineacetamide

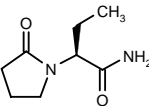
(-)-2(S)-(2-Oxopyrrolidin-1-yl)butyramide

Etiracetam *levo*-isomer⁺

L-059

SIB-S1

UCB-L059



C8 H14 N2 O2; Mol wt: 170.2106

ACTION – Antiepileptic drug whose mechanism of action remains unknown.

INDICATION – Adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy.

PRESENTATION – Tablets, 250, 500 and 750 mg.

PROPRIETARY NAME – Keppra (US).

SOURCE – UCB.

RECENT REFERENCES

1. Ben-Menachem, E. "Proof of principle" study to evaluate efficacy and safety of levetiracetam (1500 mg, bid) monotherapy in patients with refractory focal epilepsy. Epilepsia 1999, 40(Suppl. 7): Abst 3.213.

2. Ben-Menachem, E. et al. Evaluation of the efficacy and tolerability of levetiracetam (LEV) monotherapy in epileptic patients with complex partial onset seizures. Epilepsia 1999, 40(Suppl. 2): 249.

3. Betts, T. Levetiracetam (LEV) in partial seizures: Pooled data from 3 double-blind placebo controlled studies. Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.06.03.

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5. Browne, T.R. et al. Absence of pharmacokinetic drug interaction of levetiracetam with phenytoin in patients with epilepsy determined by new technique. J Clin Pharmacol 2000, 40(6): 590.

6. Cramer, J.A. et al. Effect of levetiracetam on epilepsy-related quality of life. Epilepsia 2000, 41(7): 868.

7. Cramer, J.A. et al. Short-term treatment with levetiracetam enhances health-related quality of life in patients with refractory epilepsy. Epilepsia 1999, 40(Suppl. 2): 98.

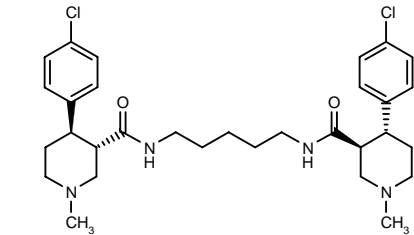
8. Crawford, P. et al. Levetiracetam (LEV) for the treatment of refractory epilepsy: Tolerability and efficacy as add-on treatment without uptitration period. Epilepsia 1999, 40(Suppl. 2): 248.

9. Creech, J. et al. Levetiracetam in intractable partial epilepsy: Efficacy of add-on therapy and patient retention. Epilepsia 1999, 40(Suppl. 7): Abst 2.259.

10. Doheny, H.C. et al. Blood and cerebrospinal fluid pharmacokinetics of the novel anticonvulsant levetiracetam (Ucb L059) in the rat. Epilepsy Res 1999, 34(2-3): 161.

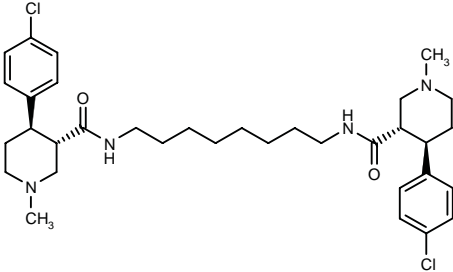
290028^{1,2}

(-)-*trans*-*N,N'*-(1,5-Pentanediy)bis[4-(4-chlorophenyl)-1-methylpiperidine-3-carboxamide]



C31 H42 Cl2 N4 O2; Mol wt: 573.6048

ACTION – Potent and selective 5-HT reuptake inhibitor ($K_i = 1.2$ nM) with more than 1,000-fold selectivity over the dopamine transporter ($K_i = 1960$ nM) and about 300-fold selectivity over the noradrenaline transporter ($K_i = 393$ nM). Potentially useful for the treatment of depression and related psychological disorders. Another related compound is:



290026:² C34 H48 Cl2 N4 O2

SOURCES – Georgetown University, Washington, DC (US); University of Texas Medical Branch at Galveston, Galveston, TX (US).

REFERENCES

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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

LEVETIRACETAM

Rec INN

113936

(-)-(S)- α -Ethyl-2-oxo-1-pyrrolidineacetamide

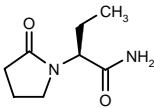
(-)-2(S)-(2-Oxopyrrolidin-1-yl)butyramide

Etiracetam *levo*-isomer⁺

L-059

SIB-S1

UCB-L059



C8 H14 N2 O2; Mol wt: 170.2106

ACTION – Antiepileptic drug whose mechanism of action remains unknown.

INDICATION – Adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy.

PRESENTATION – Tablets, 250, 500 and 750 mg.

PROPRIETARY NAME – Keppra (US).

SOURCE – UCB.

RECENT REFERENCES

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2. Ben-Menachem, E. et al. Evaluation of the efficacy and tolerability of levetiracetam (LEV) monotherapy in epileptic patients with complex partial onset seizures. Epilepsia 1999, 40(Suppl. 2): 249.
3. Betts, T. Levetiracetam (LEV) in partial seizures: Pooled data from 3 double-blind placebo controlled studies. Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.06.03.
4. Betts, T. et al. Efficacy and tolerability of levetiracetam (LEV) as add-on treatment in refractory seizures: No need for an up-titration step. J Neurol 1999, 246(Suppl. 1): Abst 156.
5. Browne, T.R. et al. Absence of pharmacokinetic drug interaction of levetiracetam with phenytoin in patients with epilepsy determined by new technique. J Clin Pharmacol 2000, 40(6): 590.
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9. Creech, J. et al. Levetiracetam in intractable partial epilepsy: Efficacy of add-on therapy and patient retention. Epilepsia 1999, 40(Suppl. 7): Abst 2.259.
10. Doheny, H.C. et al. Blood and cerebrospinal fluid pharmacokinetics of the novel anticonvulsant levetiracetam (Ucb L059) in the rat. Epilepsy Res 1999, 34(2-3): 161.

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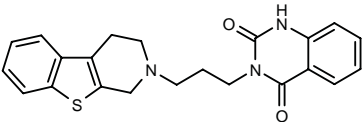
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†Drug Data Rep 1986, 008(06): 0529.

TREATMENT OF EXTRAPYRAMIDAL
MOVEMENT DISORDERS

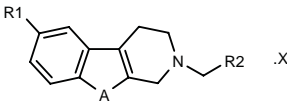
288712

3-[3-(1,2,3,4-Tetrahydro[1]benzothieno[2,3-*c*]pyridin-2-yl)propyl]quinazoline-2,4(1*H*,3*H*)-dione



C22 H21 N3 O2 S; Mol wt: 391.4929

ACTION – α_2 -Adrenoceptor antagonist, as demonstrated *in vitro* in CHO cells expressing cloned human α_{2A} -, α_{2B} - and α_{2C} -adrenoceptors. Potentially useful for the treatment of depression, cognition disorders, diabetes mellitus, sexual dysfunction, glaucoma and, particularly, for the treatment of Parkinson’s disease. Other compounds from this series of tricyclic Δ^3 -piperidines are:



Compound	R1	R2	A	X	Formula
288713	H	2,4-dioxo-1,2,3,4-tetrahydro-3-quinazoliny-(CH2)3	S		C ₂₃ H ₂₃ N ₃ O ₂ S
288714	H	2,4-dioxo-1,2,3,4-tetrahydro-3-quinazoliny-(CH2)3	O		C ₂₃ H ₂₃ N ₃ O ₃
288715	H	2-oxo-2,3-dihydro-1-benzimidazolyl-CH2CH2	S		C ₂₁ H ₂₁ N ₃ OS
288716	H	2-oxo-2,3-dihydro-1-benzimidazol-yl-(CH2)3	O		C ₂₂ H ₂₃ N ₃ O ₂
288717	Me	2-oxo-2,3-dihydro-1-benzimidazolyl-(CH2)3	O	HCl	C ₂₃ H ₂₅ N ₃ O ₂ .HCl
288718	Me	1,2-benzisoxazol-3-yl-NH(CH2)3	O	HCl	C ₂₃ H ₂₅ N ₃ O ₂ .HCl

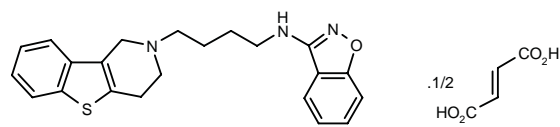
SOURCE – Janssen.

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1. Kennis, L.E.J. et al. (Janssen Pharmaceutica NV) *Tricyclic Δ^3 -piperidines as α_2 -antagonists*. WO 0020421.

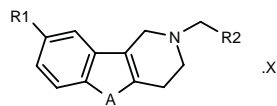
288719

N-[4-(1,2,3,4-Tetrahydro[1]benzothieno[3,2-c]pyridin-2-yl)butyl]-1,2-benzisoxazol-3-amine hemifumarate



C22 H23 N3 O S . 1/2C4 H4 O4; Mol wt: 435.5455

ACTION – α_2 -Adrenoceptor antagonist, as demonstrated *in vitro* in CHO cells expressing cloned human α_{2A} -, α_{2B} - and α_{2C} -adrenoceptors. Potentially useful for the treatment of depression, cognition disorders, diabetes mellitus, sexual dysfunction, glaucoma and, particularly, for the treatment of Parkinson's disease. Other compounds from this series of tricyclic Δ^3 -piperidines are:



Compound	R1	R2	A	X	Formula
288720	H	3-indolyl-CH2	O		C ₂₁ H ₂₀ N ₂ O
288721	H	2-oxo-2H-1-benzopyran-3-yl-CH2	O		C ₂₂ H ₁₉ NO ₃
288722	H	3-indolyl-CH2	S		C ₂₁ H ₂₀ N ₂ S
288723	Me	1,2-benzisoxazol-3-yl-NH(CH2)3	S	HCl	C ₂₃ H ₂₅ N ₃ OS.HCl
288724	H	4-(4-F-PhCONH)-Ph	O		C ₂₅ H ₂₁ FN ₂ O ₂
288725	H	3-(4-F-PhCONH)-Ph	O	HCl	C ₂₅ H ₂₁ FN ₂ O ₂ .HCl
288726	H	1,2-benzisoxazol-3-yl-NH(CH2)3	O	hemi-fumarate	C ₂₂ H ₂₃ N ₃ O ₂ .1/2C ₄ H ₄ O ₄
288727	H	3-(4-F-PhCO)-Ph	O	HCl	C ₂₅ H ₂₀ FN ₂ O ₂ .HCl
288728	H	4-(4-F-PhCO)-Ph	O	HCl	C ₂₅ H ₂₀ FN ₂ O ₂ .HCl

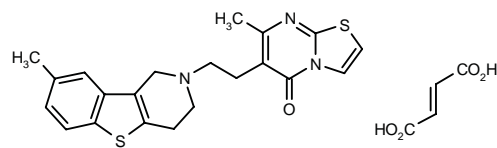
SOURCE – Janssen.

REFERENCES

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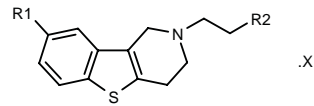
288729

7-Methyl-6-[2-(8-methyl-1,2,3,4-tetrahydro[1]benzothieno[3,2-c]pyridin-2-yl)ethyl]-5H-thiazolo[3,2-a]pyrimidin-5-one fumarate



C21 H21 N3 O S2 . C4 H4 O4; Mol wt: 511.6205

ACTION – α_2 -Adrenoceptor antagonist, as demonstrated *in vitro* in CHO cells expressing cloned human α_{2A} -, α_{2B} - and α_{2C} -adrenoceptors. Potentially useful for the treatment of depression, cognition disorders, diabetes mellitus, sexual dysfunction, glaucoma and, particularly, for the treatment of Parkinson's disease. Other compounds from this series of benzothieno[3,2-c]-pyridines are:



Compound	R1	R2	X	Formula
288731	H	2-oxo-2,3-dihydro-1-benzimidazolyl-CH2CH2		C ₂₂ H ₂₃ N ₃ OS
288734	H	theophyllin-7-yl-CH2CH2	fumarate	C ₂₂ H ₂₅ N ₃ O ₂ S.C ₄ H ₄ O ₄
288735	H	2-Ph-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl	2HCl	C ₂₇ H ₂₃ N ₃ OS.2HCl
288737	Me	2-Me-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl	.2HCl.H2O	C ₂₃ H ₂₃ N ₃ OS.2HCl.H2O
288741	H	2-benzothiazolyl-NHCH2CH2	2HCl	C ₂₂ H ₂₃ N ₃ S ₂ .2HCl
288742	H	2-Me-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl	hemifumarate	C ₂₂ H ₂₁ N ₃ OS.1/2C ₄ H ₄ O ₄

SOURCE – Janssen.

REFERENCES

1. Kennis, L.E.J. et al. (Janssen Pharmaceutica NV) *Benzothieno[3,2-c]pyridines as α₂ antagonists*. WO 0020422.

THERAPY OF IMMUNOLOGIC NEUROMUSCULAR DISORDERS

κ-A671

288874

ACTION – A representative compound from a series of κA conopeptides isolated from the venom of mollusks of the genus *Conus* that blocks the flow of potassium ions through voltage-gated potassium channels, as demonstrated in neonatal rat cortex primary cultures. Potentially useful for the treatment of a broad range of disorders including multiple sclerosis and other demyelinating diseases, spinal cord injury, Huntington's chorea, neuropathies, cardiovascular disorders, hyperglycemia, immunosuppression, cocaine addiction, cancer, cognitive dysfunction and for reversing the actions of curare and other neuromuscular blocking drugs.

SOURCES – Cognetix; Salk Institute for Biological Studies, La Jolla, CA (US); University of Utah, Salt Lake City, UT (US).

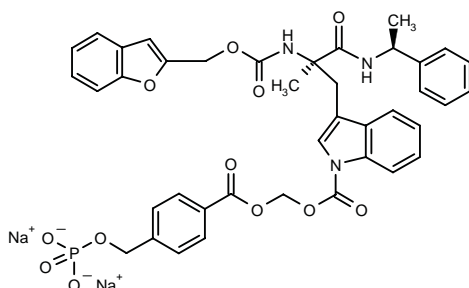
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TREATMENT OF NAUSEA AND VOMITING

289888

3-[2(*R*)-(Benzofuran-2-ylmethoxycarboxamido)-2-methyl-3-oxo-3-[1(*S*)-phenylethylamino]propyl]-1 *H*-indole-1-carboxylic acid 4-(phosphonooxymethyl)benzoyloxymethyl ester disodium salt



C40 H36 N3 Na2 O12 P; Mol wt: 827.6874

ACTION – Potential antiemetic agent, a phosphate prodrug of the potent and selective tachykinin NK₁ receptor antagonist PD-154075⁺. The prodrug exhibited significantly increased aqueous solubility (58 mg/ml versus < 1 µg/ml for PD-154075), sufficient stability in aqueous solutions and extensive bioconversion to PD-154075 *in vivo* (59.5 %) following i.v. administration to rats.

SOURCE – Pfizer.

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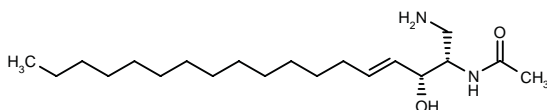
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⁺Drug Data Rep 1997, 019(03): 0214.

COGNITION-ENHANCING DRUGS

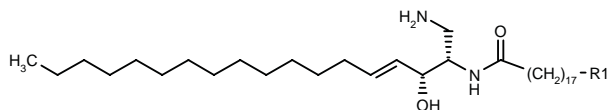
289248

N-[1(*S*)-(Aminomethyl)-2(*R*)-hydroxy-3(*E*)-heptadecenyl]-acetamide



C20 H40 N2 O2; Mol wt: 340.5480

ACTION – Sphingomyelinase inhibitor potentially useful in the treatment of dementia and memory disorders, and as an antiinflammatory agent. A representative compound from a series of ceramide derivatives, wherein the following are also included:



Compound	R1	Formula
289249	H	C ₃₆ H ₇₂ N ₂ O ₂
289250	C6H13	C ₄₂ H ₈₄ N ₂ O ₂

SOURCE – Otsuka.

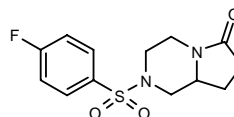
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DM-232

288037

2-(4-Fluorophenylsulfonyl)perhydropyrrolo[1,2-*a*]pyrazin-6-one



C13 H15 F N2 O3 S; Mol wt: 298.3365

ACTION – Nootropic agent with *in vivo* pharmacological activity very similar to that of piracetam, but much higher potency. Compound was able to reverse the amnesia induced by scopolamine in the passive avoidance test in mice at doses as low as 0.001 mg/kg s.c., being at least 1,000-fold more potent than piracetam. In addition to scopolamine, compound was also able to reverse amnesia induced by mecamlamine, baclofen and clonidine. At doses 1,000-fold higher than the minimal effective dose, it did not show any effect on motor coordination or spontaneous motility.

SOURCE – Università degli Studi di Firenze, Firenze (IT).

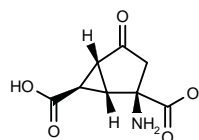
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TREATMENT OF CEREBROVASCULAR DISEASES

288555

(+)-(1*S**,2*R**,5*R**,6*R**)-2-Amino-4-oxobicyclo[3.1.0]-hexane-2,6-dicarboxylic acid



C8 H9 N O5; Mol wt: 199.1611

ACTION – Group II metabotropic glutamate receptor (mglu₂) modulator, as demonstrated in a functional assay by an ED₅₀ value of 0.736 nM for inhibition of forskolin-stimulated cAMP accumulation in CHO cells expressing the mglu₂ receptor. Potentially useful in the treatment of psychiatric and neurological disorders such as anxiety, schizophrenia, depression, epilepsy, drug dependence, memory disorders, Alzheimer’s disease, Huntington’s chorea, Parkinson’s disease, muscle rigidity, cerebral ischemia or head and spinal cord trauma. A representative compound from a series of 4-substituted-2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives.

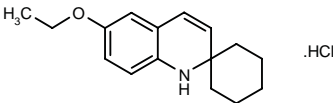
SOURCE – Taisho.

REFERENCES

1. Nakazato, A. et al. (Taisho Pharmaceutical Co., Ltd.) *4-Substd.-2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivs. and pharmaceutical compsns.* JP 2000072731.

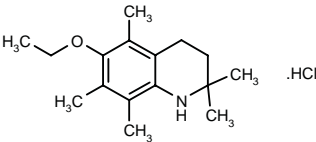
288792

6'-Ethoxyspiro[cyclohexane-1,2'(1'*H*)-quinoline] hydrochloride



C16 H21 N O . HCl; Mol wt: 279.8088

ACTION – Agent for the treatment of cerebral ischemia, epilepsy, neurodegenerative disorders such as Alzheimer’s disease, Pick’s disease, Parkinson’s disease and Huntington’s disease, as well as atherosclerosis and cataracts, with antioxidant activity, particularly on the CNS, and devoid of hypothermic effects. *In vitro*, compound completely protected against L-homocysteinic acid-induced cytotoxicity in murine hippocampal HT-22 cells at 0.5 μM. *In vivo*, it produced 70-100% protection against *tert*-butylhydroperoxide-induced lethality in mice at 150 mg/kg i.p. and exhibited neuroprotective effects in a rat model of global cerebral ischemia. In addition, it was shown to reduce by 3-fold kainic acid-induced neurotoxicity in rats at 150 mg/kg i.p. Another specifically claimed compound from this series of dihydro- and tetrahydroquinoline derivatives is:



289328: C16 H25 N O . HCl

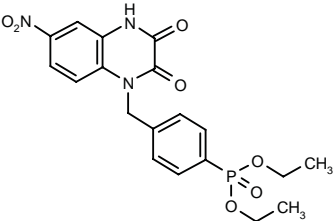
SOURCE – Servier.

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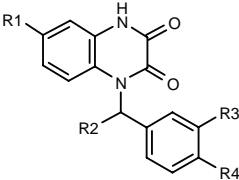
289072

4-(6-Nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-1-yl-methyl)phenylphosphonic acid diethyl ester



C19 H20 N3 O7 P; Mol wt: 433.3550

ACTION – Excitatory amino acid antagonist with high and specific affinity for AMPA receptors, expected to be useful for the treatment of Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, epilepsy, hypoglycemia, psychosis, muscular rigidity, emesis, pain, anoxia and ischemia-related deficits. Other specifically claimed quinoxaline-phosphonic acid derivatives are:



Compound	R1	R2	R3	R4	Formula
289073	NO2	H	H	PO3H2	C ₁₅ H ₁₂ N ₃ O ₇ P
289074	CF3	PO3H2	H	H	C ₁₆ H ₁₂ F ₃ N ₂ O ₅ P
289075	NO2	H	PO3H2	H	C ₁₅ H ₁₂ N ₃ O ₇ P

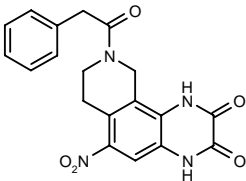
SOURCE – Schering AG.

REFERENCES

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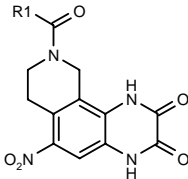
289076

6-Nitro-9-(2-phenylacetyl)-1,2,3,4,7,8,9,10-octahydro-pyrido[3,4-*f*]quinoxaline-2,3-dione



C19 H16 N4 O5; Mol wt: 380.3584

ACTION – Antagonist of glutamate receptors including both NMDA and non-NMDA (AMPA and kainate) receptors, with IC₅₀ values of 0.84 and 1.62 μM, respectively, when tested for its binding affinity for AMPA and kainate receptors. It was active in the maximal electroshock seizure assay in mice. Potentially useful as a neuroprotective agent, particularly for the treatment of cerebral ischemia, as well as for treating epilepsy, schizophrenia, neuropathic pain and neurodegenerative disorders. Other exemplified *N*-substituted azacycloalkyl-quinoxalinediones include the following:



Compound	R1	Formula
289077	1-(t-BuOCO)-4-Pip	C ₂₂ H ₂₇ N ₅ O ₇
289078	Ph	C ₁₈ H ₁₄ N ₄ O ₅
289079	cyclohexyl	C ₁₈ H ₂₀ N ₄ O ₅
289080	4-Cl-Ph	C ₁₈ H ₁₃ ClN ₄ O ₅
289081	4-Cl-PhCH2	C ₁₉ H ₁₅ ClN ₄ O ₅

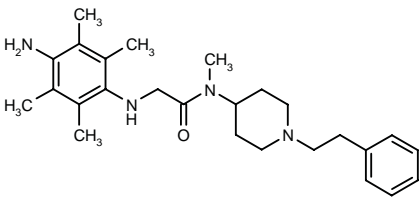
SOURCE – Pfizer.

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1. Bigge, C.F. et al. (Pfizer Inc.) *Glutamate (AMPA/kainate) receptor antagonists: N-Substd. fused azacycloalkylquinoxalinediones*. US 6057313.

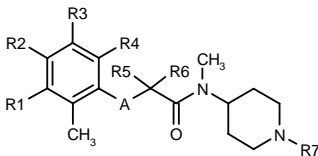
289356

2-(4-Amino-2,3,5,6-tetramethylphenylamino)-*N*-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide



C26 H38 N4 O; Mol wt: 422.6132

ACTION – Neuroprotective agent that acts by inducing the Ca²⁺-binding protein calbindin D28Kd, potentially useful for the treatment of brain functional disorders due to ischemic conditions and cerebral organic disorders such as senile dementia, cerebral injury, Alzheimer’s disease, sequelae of brain surgery, Parkinson’s disease and amyotrophic lateral sclerosis. It demonstrated cyto-protective effect against glutamate-induced cell death using cerebral cortical neurons and induced calbindin D28Kd *in vitro*. It was active in suppressing cerebral edema in rats at 1 and 3 mg/kg i.v. Other exemplified aminophenoxyacetic acid derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	A	Formula
289357	Me	NH2	Me	H	H	H	CH2CONHPh	O	C ₂₅ H ₃₄ N ₄ O ₃
289358	Me	NH2	Me	H	Me	Me	CH2CONHPh	O	C ₂₇ H ₃₈ N ₄ O ₃
289359	Me	NH2	Me	Me	H	H	CH2COPh	NH	C ₂₆ H ₃₆ N ₄ O ₂
289360	H	Me	NH2	Me	H	H	COPh	NH	C ₂₄ H ₃₂ N ₄ O ₂
289361	H	Me	NH2	Me	H	H	Bu	NH	C ₂₁ H ₃₆ N ₄ O

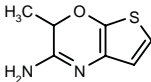
SOURCE – Suntory.

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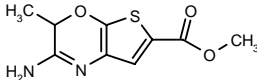
289489

3-Methyl-3*H*-thieno[2,3-*b*][1,4]oxazin-2-ylamine



C7 H8 N2 O S; Mol wt: 168.2192

ACTION – Nitric oxide synthase (NOS) inhibitor with potential in the treatment of NO-mediated diseases such as neurodegenerative, inflammatory, autoimmune and cardiovascular disorders. Another specifically claimed compound from this series of thienooxazine derivatives is:



289491: C9 H10 N2 O3 S

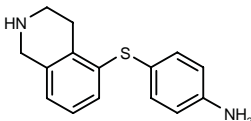
SOURCE – Schering AG.

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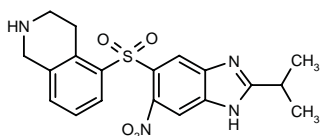
289543

4-(1,2,3,4-Tetrahydroisoquinolin-5-ylsulfanyl)phenylamine



C15 H16 N2 S; Mol wt: 256.3714

ACTION – Neuroprotective agent that acts by inhibiting neuronal apoptosis, as demonstrated by inhibiting colchicine-induced nerve cell death using human neuroblastoma SH-SY5Y cells. Another 1,2,3,4-tetrahydroisoquinoline derivative is:



289544: C₁₉ H₂₀ N₄ O₄ S

SOURCE – Snow Brand.

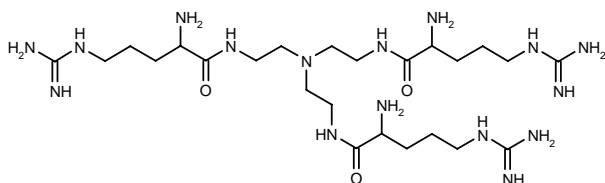
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1. Ishiguro, S. et al. (Snow Brand Milk Products Co., Ltd.) *Novel 1,2,3,4-tetrahydro isoquinoline derivs.* JP 2000109463.

CYP-PA1

289648

2-Amino-5-guanidino-*N*-[2-[bis[2-(2-amino-5-guanidino-pentanoylamino)ethyl]amino]ethyl]pentanamide



C₂₄ H₅₄ N₁₆ O₃; Mol wt: 614.7996

ACTION – Neuroprotective agent, a representative compound from a series of polyguanidino derivatives that can penetrate the blood–brain barrier and block presynaptic N- and P/Q-type calcium channels, thereby reducing excitotoxic damage in the CNS. *In vitro*, compound exhibited IC₅₀ values of 3.60, 2.10 and 0.40 μM for inhibition of [¹²⁵I]-conotoxin GVIA, -conotoxin MVIIA and -conotoxin MVIIIC binding to N-, N- and P/Q-type channels, respectively, in rat brain membrane preparations. *In vivo*, it exhibited potent neuroprotective effects in a global cerebral ischemia model in gerbils at 20 mg/kg i.p. when given both pre- and postocclusion, and it was devoid of toxicity in mice at 200 mg/kg i.p. Potentially useful for the treatment of patients suffering from ischemic or hypoxic crises (stroke, cardiac arrest, loss of blood, suffocation, etc.), as well as for suppressing other types of unwanted excessive neuronal activation such as neuropathic pain.

SOURCE – Questcor.

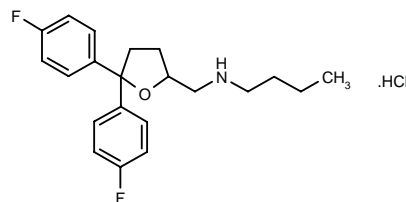
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LY-393615

289566

N-[5,5-Di(4-Fluorophenyl)tetrahydrofuran-2-ylmethyl]-*N*-butylamine hydrochloride



C₂₁ H₂₅ F₂ N O . HCl; Mol wt: 381.8914

ACTION – Broad-spectrum neuronal calcium channel blocker with neuroprotective properties in various *in vitro* and *in vivo* models of cerebral ischemia. In an *in vitro* model of hypoxic–hypoglycemic insult in rat brain slices, compound (10 μM) was able to prevent ischemic injury in both striatum and cerebral cortex.

SOURCE – Lilly.

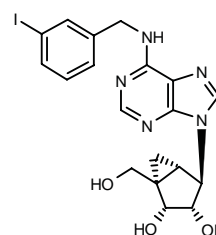
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MRS-1743

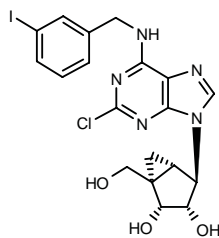
289147

(1*R*,2*R*,3*S*,4*R*,5*S*)-1-(Hydroxymethyl)-4-[6-(3-iodobenzyl-amino)-9*H*-purin-9-yl]bicyclo[3.1.0]hexane-2,3-diol



C₁₉ H₂₀ I N₅ O₃; Mol wt: 493.2990

ACTION – Adenosine A₃ receptor ligand with high affinity (K_i = 4.13 nM for human receptor) and high selectivity over A_{2B} and A_{2A} receptors (K_i = 12,100 and 601 nM, respectively) and 17-fold selectivity versus rat A₁ receptors (K_i = 69 nM). In *in vitro* functional tests, compound exhibited partial agonist activity with high functional potency (EC₅₀ = 0.70 nM for stimulation of [³⁵S]-GTP-γS binding in CHO cells stably expressing human brain A₃ receptors; efficacy = 45%). Potentially useful for the treatment of cerebral or cardiac ischemia. Another methanocarba analogue of adenosine is:



MRS-1760 [289148]: C₁₉ H₁₉ Cl I N₅ O₃

SOURCES – National Cancer Institute, Bethesda, MD (US); National Institutes of Health, Bethesda, MD (US).

REFERENCES

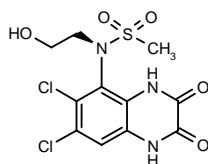
1. Jacobson, K.A. et al. *Methanocarba analogues of purine nucleosides as potent and selective adenosine receptor agonists*. J Med Chem 2000, 43(11): 2196.

UK-240255

288189

(a*R*)-*N*-(6,7-Dichloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)-*N*-(2-hydroxyethyl)methanesulfonamide

UK-212189 (as racemic)



C₁₁ H₁₁ Cl₂ N₃ O₅ S; Mol wt: 368.1959

ACTION – Potent glycine-site NMDA receptor antagonist found to be active in the mouse wild running model (ED₅₀ = 3 mg/kg), as well as in a rat middle cerebral artery occlusion model, where it was as effective as the reference MK-801. Phase I clinical studies indicated that the maximal tolerated dose of compound is 4 mg/kg, providing plasma concentrations of 6.5 µg/kg and a half life of 1 h. Potentially useful for the treatment of stroke.

SOURCE – Pfizer.

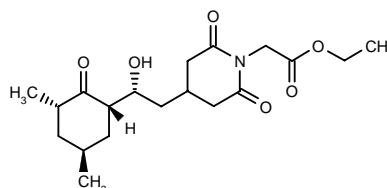
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3. Norman, P. *Rational approaches to new drug design in the U.K.* Drug News Perspect 2000, 13(4): 0245.

MISCELLANEOUS NEUROLOGIC DRUGS

280331

2-[4-[2(*R*)-[3(*S*),5(*R*)-Dimethyl-2-oxo-1(*S*)-cyclohexyl]-2-hydroxyethyl]-2,6-dioxopiperidin-1-yl]acetic acid ethyl ester



C₁₉ H₂₉ N O₆; Mol wt: 367.4391

ACTION – Cycloheximide derivative with the ability to competitively inhibit human FKBP12 with a potency comparable to the parent compound (K_i = 4.1 and 3.4 µM, respectively). Compound was found to have an approximately 1,000-fold weaker inhibitory effect on eukaryotic protein synthesis (IC₅₀ = 115 and 0.1 µM, respectively) and was less cytotoxic than the parent compound against eukaryotic cell lines including mouse L-929 fibroblasts (IC₅₀ = 76.6 and < 0.39 µg/ml, respectively) and leukemia K-562 cells (IC₅₀ = 64.9 and < 0.30 µg/ml, respectively). In a rat sciatic nerve neurotomy model, it significantly accelerated nerve regeneration when applied directly to the anastomoses at a dose of 30 mg/kg. Potentially useful for the treatment of human nerve injuries and neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease.

SOURCES – Friedrich-Schiller-Universität Jena, Jena (DE); Hans Knöll Institute of Natural Product Research, Jena (DE); Max-Planck Research Unit, Halle/Salle (DE).

REFERENCES

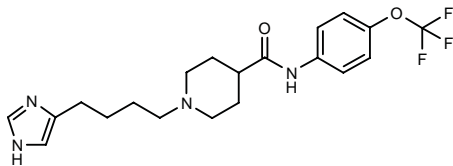
1. Fischer, G. et al. (Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V.; Hans Knöll Institute for Natural Product Research) *Cyclohexamide derivs. which influence the regeneration of neural tissue*. WO 0026188.
2. Christner, C. et al. *Synthesis and cytotoxic evaluation of cycloheximide derivatives as potential inhibitors of FKBP12 with neuroregenerative properties*. J Med Chem 1999, 42(18): 3615.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

289322

1-[4-(1*H*-Imidazol-4-yl)butyl]-*N*-[4-(trifluoromethoxy)-phenyl]piperidine-4-carboxamide



C20 H25 F3 N4 O2; Mol wt: 410.4375

ACTION – A representative compound from a series of *N*-(imidazolylalkyl)substituted cyclic amines that acts as a histamine H₃ receptor ligand, giving a K_i value of 2 nM in a binding assay using guinea pig brain membranes and a pA₂ of 9.3. Potentially useful in the treatment of allergy, inflammation, hypertension, glaucoma, sleep disorders, gastrointestinal motility disorders, CNS hypo- or hyperactivity, Alzheimer’s disease, schizophrenia and migraine.

SOURCE – Schering-Plough.

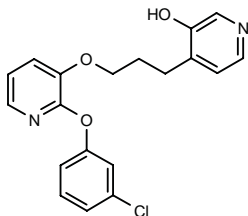
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ASTHMA THERAPY

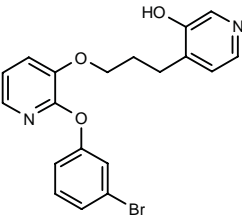
288661

4-[3-[2-(3-Chlorophenoxy)pyridin-3-yloxy]propyl]pyridin-3-ol



C19 H17 Cl N2 O3; Mol wt: 356.8073

ACTION – Antiinflammatory, antiallergic, antiasthmatic and bronchodilating agent, a potent and selective inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 15.7 nM against guinea pig enzyme). *In vivo*, it dose-dependently inhibited antigen-induced bronchoconstriction in guinea pigs following oral administration (3-30 mg/kg). Another compound from this series of 2,3-disubstituted pyridine derivatives is:



288662: C19 H17 Br N2 O3

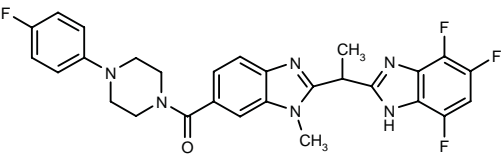
SOURCE – Dainippon Pharmaceutical.

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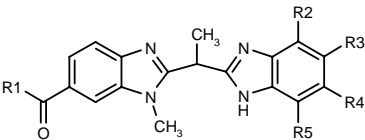
288760

1-[4-(4-Fluorophenyl)piperazin-1-yl]-1-[1-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-6-yl]methanone



C28 H24 F4 N6 O; Mol wt: 536.5306

ACTION – Tryptase inhibitor (K_i’ = 3.0 nM against human enzyme) with high oral bioavailability (72, 74 and 100%, respectively, in rats, dogs and monkeys), potentially useful in the treatment of diseases associated with tryptase activity including allergic, inflammatory and related immunological diseases, in particular asthma, allergic rhinitis, allergic conjunctivitis and allergic dermatitis. Other compounds from this series of bis-benzimidazoles include the following:



Compound	R1	R2	R3	R4	R5	Formula
288762	4-(4-F-Ph)-1-Piz	H	F	OH	H	C ₂₈ H ₂₆ F ₂ N ₆ O ₂
288764	4-(2-NH2-4-F-Ph)-1-Piz	F	F	H	F	C ₂₈ H ₂₅ F ₄ N ₇ O
288765	4-F-PhOCH2CH2NH	F	H	F	H	C ₂₆ H ₂₂ F ₃ N ₅ O ₂

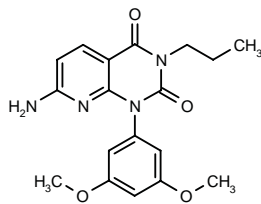
SOURCE – Bayer.

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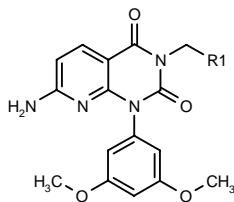
288774

7-Amino-1-(3,5-dimethoxyphenyl)-3-propylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione



C18 H20 N4 O4; Mol wt: 356.3800

ACTION – Antiasthmatic agent with excellent broncho-dilating activity, as demonstrated by an EC₅₀ value of 0.4 μM for inducing relaxation of histamine-contracted guinea pig airways smooth muscle, being more potent than theophylline (EC₅₀ = 51 μM). Compound showed an excellent safety profile in mice following oral administration of 300 and 1000 mg/kg, as well as good pharmacokinetic properties, with a half-life of 28.4 h following administration of a dose of 30 mg/kg p.o. to guinea pigs. Other compounds from this series of 7-aminopyrido[2,3-*d*]pyrimidine derivatives include the following:



Compound	R1	Formula
288775	Me	C ₁₇ H ₁₈ N ₄ O ₄
288778	Pr	C ₁₉ H ₂₂ N ₄ O ₄
288779	i-Pr	C ₁₉ H ₂₂ N ₄ O ₄
288781	4-Pyr	C ₂₁ H ₁₉ N ₅ O ₄

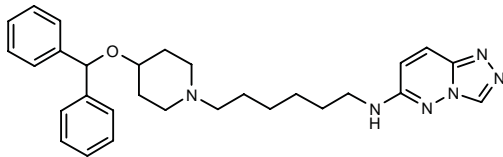
SOURCE – Nippon Zoki.

REFERENCES

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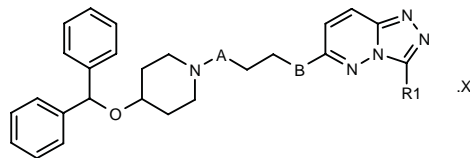
288838

N-[6-[4-(Diphenylmethoxy)piperidin-1-yl]hexyl]-*N*-(1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)amine

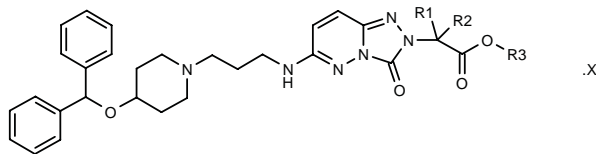


C29 H36 N6 O; Mol wt: 484.6444

ACTION – Agent with antiallergic, antihistaminic, eosinophil chemotaxis-inhibitory, antiinflammatory and PAF-antagonist effects and potential for the treatment or prevention of asthma and related disorders. Compound inhibited LTB₄-induced guinea pig eosinophil chemotaxis (60% inhibition at 10 μM) and histamine-induced increases in vascular permeability in guinea pigs (91% inhibition at 3 mg/kg p.o.). Other compounds from this series of fused pyridazine derivatives include the following:



Compound	R1	A	B	X	Formula
288839	H	-(CH2)4-	O	fumarate	C ₂₉ H ₃₅ N ₅ O ₂ ·C ₄ H ₄ O ₄
288840	t-Bu	-CH2-	O		C ₃₀ H ₃₇ N ₅ O ₂
288841	CO2H	-CH2-	NH		C ₂₇ H ₃₀ N ₆ O ₃



Compound	R1	R2	R3	X	Formula
288842	H	H	Et		C ₃₀ H ₃₆ N ₆ O ₄
288843	Me	Me	Et	HCl	C ₃₂ H ₄₀ N ₆ O ₄ ·HCl
288844	Me	Me	H		C ₃₀ H ₃₆ N ₆ O ₄

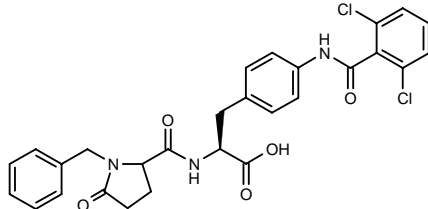
SOURCE – Takeda.

REFERENCES

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288884

N-(1-Benzyl-5-oxopyrrolidin-2-ylcarbonyl)-4-(2,6-dichlorobenzamido)-*L*-phenylalanine



C28 H25 Cl2 N3 O5; Mol wt: 554.4275

ACTION – Antiinflammatory agent, an inhibitor of the VCAM-1/VLA-4 interaction (IC₅₀ = 0.37 and 12 nM in the ELISA and Ramos cell assays, respectively), potentially useful for the treatment of asthma and rheumatoid arthritis.

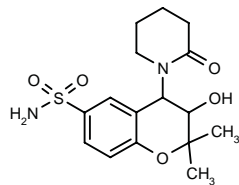
SOURCE – Roche.

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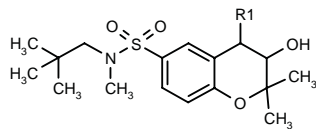
288922

3-Hydroxy-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-6-sulfonamide



C16 H22 N2 O5 S; Mol wt: 354.4248

ACTION – Potassium channel opener with potential in the treatment of obstructive or inflammatory airways diseases, hypertension, chronic cardiac insufficiency, ischemia or urinary incontinence. Compound was shown to inhibit histamine-induced airways hyperreactivity in sensitized guinea pigs following intratracheal administration with an ED₅₀ value of 4 µg/kg, while producing no significant changes in arterial blood pressure and heart rate at doses up to 10 µg/kg. Other exemplified compounds from this series of benzopyran derivatives are:



Compound	R1	Isomer	Formula
288923	2-oxo-1-Pip		C ₂₂ H ₃₄ N ₂ O ₅ S
288924	3-Pyr-CONH	trans	C ₂₃ H ₃₁ N ₃ O ₅ S

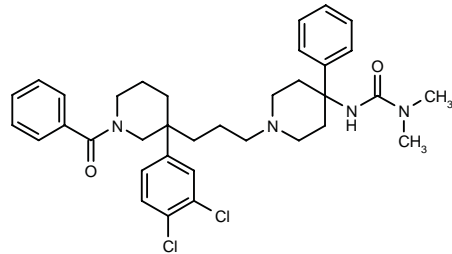
SOURCE – Novartis.

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288973

N'-[1-[3-[1-Benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl]propyl]-4-phenylpiperidin-4-yl]-*N,N*-dimethylurea



C35 H42 Cl2 N4 O2; Mol wt: 621.6488

ACTION – Selective human NK₃ receptor antagonist with potential in the treatment of respiratory disorders, CNS diseases, pain and gastrointestinal disorders. A specifically claimed compound from a series of ureido-piperidine derivatives.

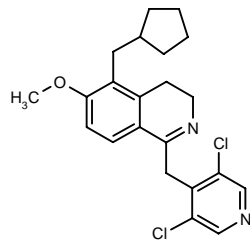
SOURCE – Sanofi-Synthélabo.

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288974

5-(Cyclopentylmethyl)-1-(3,5-dichloropyridin-4-ylmethyl)-6-methoxy-3,4-dihydroisoquinoline



C22 H24 Cl2 N2 O; Mol wt: 403.3506

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 35.9 ± 4.7 nM when tested for PDE4 inhibition in human polymorphonuclear leukocytes), expected to be useful for treating allergic and inflammatory disorders, particularly asthma, allergic rhinitis, emphysema, chronic obstructive pulmonary disease and chronic bronchitis.

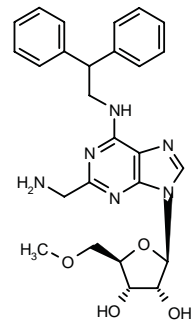
SOURCE – Zambon.

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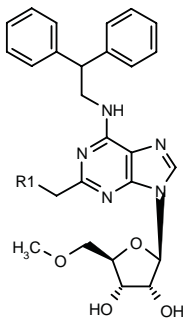
289278

2-(Aminomethyl)-*N*⁶-(2,2-diphenylethyl)-5'-*O*-methyladenosine



C26 H30 N6 O4; Mol wt: 490.5610

ACTION – Antiinflammatory agent, selective adenosine A_{2A} receptor agonist particularly useful in the treatment of respiratory tract diseases such as adult respiratory distress syndrome (ARDS), bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, chronic rhinitis and sinusitis. Other exemplified adenine derivatives include the following:



Compound	R1	Formula
289279	i-PrNH	C ₂₉ H ₃₆ N ₆ O ₄
289280	5-Me-1,2,3,4-tetrahydro-8-isoquinolinyI-SO ₂ NH	C ₃₆ H ₄₁ N ₇ O ₆ S
289281	2-MeO-PhCH ₂ NH	C ₃₄ H ₃₈ N ₆ O ₅
289282	trans-4-(PhCH ₂ NH)-cyclohexyl-NH	C ₃₉ H ₄₇ N ₇ O ₄
289283	trans-4-(MeSO ₂ NH)-cyclohexyl-NH	C ₃₃ H ₄₃ N ₇ O ₆ S
289284	1-[CH(Ph)2]-3-azetidinyI-NH	C ₄₂ H ₄₅ N ₇ O ₄
289285	CH ₂ NHCH ₂ Ph	C ₃₄ H ₃₈ N ₆ O ₄
289286	SCH ₂ Ph	C ₃₃ H ₃₆ N ₅ O ₄ S

SOURCE – Pfizer.

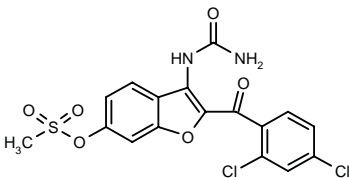
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BAY-19-8004

288544

Methanesulfonic acid 2-(2,4-dichlorophenylcarbonyl)-3-ureidobenzofuran-6-yl ester



C17 H12 Cl2 N2 O6 S; Mol wt: 443.2618

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 67 nM) with potent antiinflammatory activity in several preclinical models of bronchial asthma. In a model of allergen-induced asthma in nonhuman primates (cynomolgus monkeys), compound (0.1 mg/kg/day p.o. for 8 days) prevented the development of airways hyper-responsiveness to methacholine and partially inhibited pulmonary eosinophilia induced by multiple antigen challenge. In sensitized guinea pigs, oral pretreatment with compound inhibited the allergen-induced immediate bronchoconstriction and late (24 h) pulmonary eosinophilia (ED₅₀ = 1.5 mg/kg). In addition, compound reduced lipopolysaccharide-induced upregulation of the mucin gene MUC5 mRNA to baseline levels. Compound is currently in clinical development for the treatment of asthma and chronic obstructive pulmonary disease (COPD).

SOURCE – Bayer.

REFERENCES

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CICLESONIDE

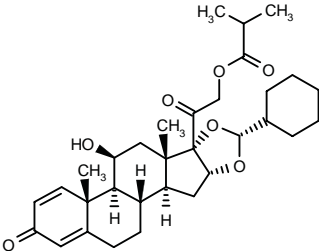
Rec INN

162123

(*R*)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with cyclohexanecarboxaldehyde,21-isobutyrate

16α-17α-[(*R*)-Cyclohexylmethylenedioxy]-11β-hydroxy-21-(isobutyryloxy)pregna-1,4-dien-3-one

BY-9010



C32 H44 O7; Mol wt: 540.6926

ACTION – Topical corticosteroid with good local antiinflammatory properties, as demonstrated in various functional *in vitro* studies and preclinical *in vivo* inflammation models. Compound exhibited low bioavailability due to its rapid systemic metabolism and particular lung tissue specificity. Phase I clinical studies demonstrated that compound was well tolerated when given orally or by inhalation to healthy volunteers, showing good local tolerability and minimal risk of systemic side effects. Phase II clinical trials in patients with allergic rhinitis demonstrated that compound significantly relieved early allergic symptoms (itching and rhinorrhea) with good tolerability, without producing local or systemic side effects. Compound is currently undergoing multinational phase II/III clinical studies in asthma patients.

SOURCES – Byk Gulden; Teijin.

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CMX5-1 MAb

288902

Humanized monoclonal antibody that specifically binds to human interleukin-5

ACTION – Humanized monoclonal antibody against human IL-5, potentially useful for blocking the activities of IL-5 and in the treatment of IL-5-related diseases, particularly eosinophilia associated with certain allergic diseases such as asthma. *In vitro*, it inhibited the binding of radiolabeled hIL-5 to recombinant hIL-5 receptor α chains in transfected COS cells with an IC_{50} value of 1.5-3.0 nM and it was found to inhibit hIL-5-induced CD11b expression in HL-60 cells with an IC_{50} value of 1467 pM. *In vivo*, it inhibited allergen-induced eosinophilia in mice at 10 mg/kg i.p.

SOURCE – Schering-Plough.

REFERENCES

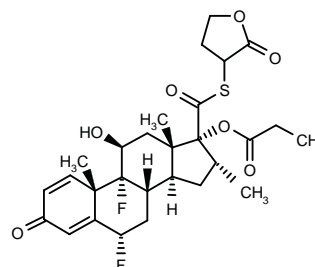
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GR-215864X*,1-6

254573

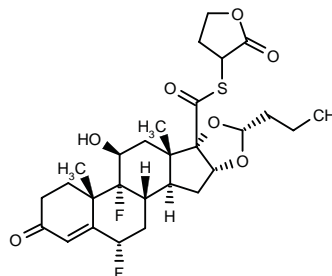
6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioic acid S-(2-oxotetrahydrofuran-3-yl)ester

GW-215864X



C28 H34 F2 O7 S; Mol wt: 552.6400

ACTION – Antiasthmatic agent, a lung-selective glucocorticoid which is rapidly metabolized in human plasma to the inactive form. In a functional assay of glucocorticoid activity in HeLa cells, compound was about 2-fold less potent than fluticasone, with an IC_{50} of 2 nM. In a rat model of albumin-induced lung eosinophilia, a single intratracheal dose of compound (750 μ g) given 4 h before ovalbumin challenge significantly inhibited eosinophil accumulation in the bronchoalveolar lavage at 48 h after challenge. Compound lacks systemic activity; 7 days of repeated intratracheal administration of compound at a dose of 750 μ g/day did not affect thymus size whereas 10-fold lower doses of budesonide produced significant thymus involution. Currently undergoing phase II clinical trials. Another related compound is:



GW-250945 [254133],1,2,4,5:** C28 H36 F2 O7 S

SOURCE – Glaxo Wellcome.

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1. Biggadike, K. and Procopiu, P.A. (Glaxo Wellcome plc) *Lactone derivs. of 17 β -carboxy, carbothio and amide androstane derivs.* JP 1999501675, WO 9724365

2. Norman, P. *Rational approaches to new drug design in the U.K.* Drug News Perspect 2000, 13(4): 0245.

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*Identified compound **254573** (see **254133**) Drug Data Rep 1997, 019(10): 0892.

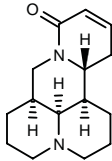
Identified compound **254133 Drug Data Rep 1997, 019(10): 0892.

SOPHOCARPINE

276709

(-)-(7a*S*,13a*R*,13b*R*,13c*S*)-2,3,6,7,7a,8,13,13a,13b,13c-Decahydro-1*H*,5*H*,10*H*-dipyrido[2,1-*f*:3,2,1-*i*][1,6]-naphthyridin-10-one

13,14-Didehydromatridin-15-one



C15 H22 N2 O; Mol wt: 246.3518

ACTION – Natural alkaloid extracted from Chinese plants of the genus *Sophora*, with bronchospasmolytic and antineoplastic activity. Compound exerted bronchodilating activity via stimulation of β -adrenoceptors without blocking the muscarinic acetylcholine receptors of bronchial smooth muscle. Compound inhibited the proliferation of several tumor cell lines and tumors *in vitro* and *in vivo* via a direct cytotoxic effect on tumor cells, without toxicity. The compound also exerts numerous other effects, including antiarrhythmic and sedative/hypnotic effects.

SOURCES – Jiangxi Traditional Chinese Medical College Pharmaceutical Factory, Nanchang (CN); Yanchi Pharmaceutical Factory, Yanchi (CN).

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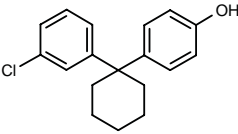
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

288582

4-[1-(3-Chlorophenyl)cyclohexyl]phenol



C18 H19 Cl O; Mol wt: 286.8001

ACTION – A representative compound from a series of cyclic derivatives active as inhibitors of endothelin-converting enzyme (ECE; IC₅₀ = 2.0 μ M against rat lung enzyme).

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

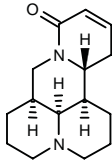
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SOPHOCARPINE

276709

(-)-(7a*S*,13a*R*,13b*R*,13c*S*)-2,3,6,7,7a,8,13,13a,13b,13c-Decahydro-1*H*,5*H*,10*H*-dipyrido[2,1-*f*:3,2,1-*i*][1,6]-naphthyridin-10-one

13,14-Didehydromatridin-15-one



C15 H22 N2 O; Mol wt: 246.3518

ACTION – Natural alkaloid extracted from Chinese plants of the genus *Sophora*, with bronchospasmolytic and antineoplastic activity. Compound exerted bronchodilating activity via stimulation of β -adrenoceptors without blocking the muscarinic acetylcholine receptors of bronchial smooth muscle. Compound inhibited the proliferation of several tumor cell lines and tumors *in vitro* and *in vivo* via a direct cytotoxic effect on tumor cells, without toxicity. The compound also exerts numerous other effects, including antiarrhythmic and sedative/hypnotic effects.

SOURCES – Jiangxi Traditional Chinese Medical College Pharmaceutical Factory, Nanchang (CN); Yanchi Pharmaceutical Factory, Yanchi (CN).

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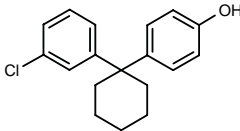
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

288582

4-[1-(3-Chlorophenyl)cyclohexyl]phenol



C18 H19 Cl O; Mol wt: 286.8001

ACTION – A representative compound from a series of cyclic derivatives active as inhibitors of endothelin-converting enzyme (ECE; IC₅₀ = 2.0 μ M against rat lung enzyme).

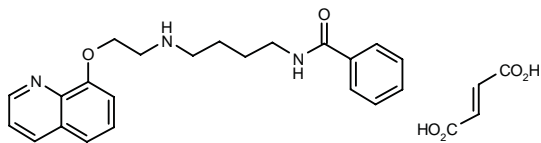
SOURCE – Sumitomo Pharmaceuticals.

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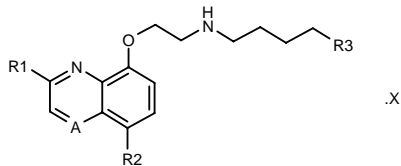
289686

N-[4-[2-(8-Quinolinyloxy)ethylamino]butyl]benzamide fumarate



C22 H25 N3 O2 . C4 H4 O4; Mol wt: 479.5301

ACTION – Agent with high affinity for 5-HT_{1A} receptors (K_i = 0.055 nM for inhibition of [³H]-8-OH-DPAT binding in rat cerebral cortical membranes), potentially useful as an antiemetic and for inhibiting gastric acid secretion, as well as for the treatment of CNS and cardiovascular disorders, particularly hypertension. Other specifically claimed compounds from this series of heteroaryloxyethylamines are:



Compound	R1	R2	R3	A	X	Formula
289687	H	H	t-BuCONH	CH	fumarate	C ₂₀ H ₂₉ N ₃ O ₂ ·C ₄ H ₄ O ₄
289688	H	H	t-BuCH ₂ CONH	CH	fumarate	C ₂₁ H ₃₁ N ₃ O ₂ ·C ₄ H ₄ O ₄
289689	H	H	cyclohexyl-CONH	CH	fumarate	C ₂₂ H ₃₁ N ₃ O ₂ ·C ₄ H ₄ O ₄
289690	H	H	1-Me-cyclohexyl-CONH	CH	fumarate	C ₂₃ H ₃₃ N ₃ O ₂ ·C ₄ H ₄ O ₄
289691	H	Cl	t-BuCH ₂ CONH	CH	fumarate	C ₂₁ H ₃₀ ClN ₃ O ₂ ·C ₄ H ₄ O ₄
289692	Me	H	t-BuCH ₂ CONH	CH	fumarate	C ₂₂ H ₃₃ N ₃ O ₂ ·C ₄ H ₄ O ₄
289693	H	H	NHCOPh	N	2HCl	C ₂₁ H ₂₄ N ₄ O ₂ ·2ClH
289694	H	H	cyclohexyl-NHCO	CH	fumarate	C ₂₂ H ₃₁ N ₃ O ₂ ·C ₄ H ₄ O ₄
289695	H	H	t-BuCH ₂ NHCO	CH	fumarate	C ₂₁ H ₃₁ N ₃ O ₂ ·C ₄ H ₄ O ₄
289696	H	H	t-BuCH ₂ NHCO	N	fumarate	C ₂₀ H ₃₀ N ₄ O ₂ ·C ₄ H ₄ O ₄

SOURCE – SCRAS.

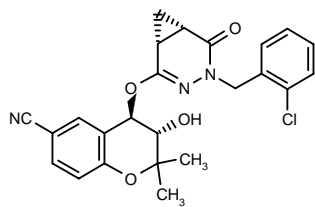
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DY-9804

288291

4(R)-[(1*R*,6*S*)-4-(2-Chlorobenzyl)-5-oxo-3,4-diazabicyclo[4.1.0]hept-2-en-2-yloxy]-3(*S*)-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-carbonitrile



C24 H22 Cl N3 O4; Mol wt: 451.9078

M.p. 188-90 °C; [α]_D²⁵ –266.6° (c 1.0, MeOH).

ACTION – Antihypertensive agent, an ATP-sensitive potassium (K_{ATP}) channel opener prodrug that exerts potent and long-lasting blood pressure-lowering activity in spontaneously hypertensive rats, where it was able to lower systolic blood pressure by 50 mmHg at the dose of 0.031 mg/kg p.o. Compound exhibited a maximal decrease in blood pressure more than 8 h after administration and its hypotensive effect lasted more than 24 h. In plasma, it was metabolized to DY-9708⁺, a potassium channel opener in isolated rat aorta.

SOURCE – Daiichi Pharmaceutical.

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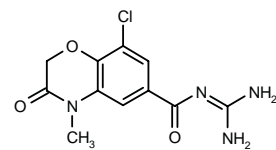
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

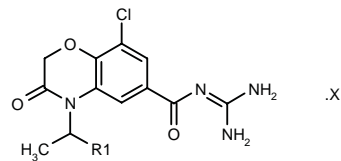
288658

N''-(8-Chloro-4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-ylcarbonyl)guanidine



C11 H11 Cl N4 O3; Mol wt: 282.6859

ACTION – Na⁺/H⁺ exchange inhibitor, a representative compound from a series of 8-substituted benzo[1,4]oxazine derivatives, wherein the following are also included:



Compound	R1	X	Formula
288659	H		C ₁₂ H ₁₃ ClN ₄ O ₃
288660	Me	HCl	C ₁₃ H ₁₅ ClN ₄ O ₃ ·HCl

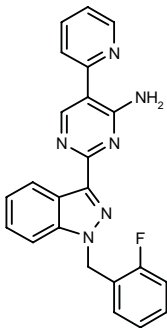
SOURCE – Kanebo (Nippon Organon).

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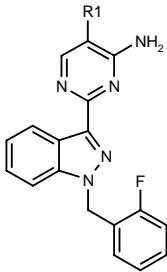
288966

2-[1-(2-Fluorobenzyl)-1*H*-indazol-3-yl]-5-(2-pyridinyl)pyrimidin-4-amine



C23 H17 F N6; Mol wt: 396.4273

ACTION – Vasorelaxant, platelet aggregation inhibitor and antihypertensive agent that acts via direct stimulation of soluble guanylate cyclase. Potentially useful for the treatment of cardiovascular disorders such as hypertension, heart failure, angina pectoris and arrhythmias, thromboembolic disorders such as myocardial infarction and stroke, restenosis following thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis and urogenital system disorders such as prostate hypertrophy, erectile dysfunction and urinary incontinence. Other exemplified compounds from this series of heterocyclyl-methyl-substituted pyrazoles are:



Compound	R1	Formula
288967	SO2Me	C ₁₉ H ₁₆ FN ₅ O ₂ S
288968	2-Pyr-SO2	C ₂₃ H ₁₇ FN ₆ O ₂ S
288970	PO(OEt)2	C ₂₂ H ₂₃ FN ₅ O ₃ P
288971	PO(O-i-Pr)2	C ₂₄ H ₂₇ FN ₅ O ₃ P
288972	CONH2	C ₁₉ H ₁₅ FN ₆ O

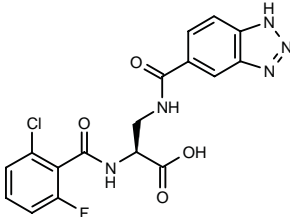
SOURCE – Bayer.

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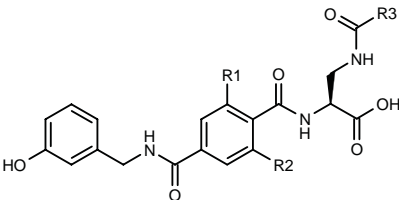
289032

3-(1*H*-Benzotriazol-5-ylcarboxamido)-2(*S*)-(2-chloro-6-fluorobenzamido)propionic acid



C17 H13 Cl F N5 O4; Mol wt: 405.7717

ACTION – ICAM-1 inhibitor expected to be useful for the treatment of acute inflammatory conditions, particularly reperfusion injury following acute myocardial infarction. The compound was found to block LFA-1 binding to ICAM-1 (IC₅₀ = 47 nM) and compete with ICAM-1 for binding to Mac-1 (IC₅₀ = 273 nM). It inhibited paw swelling in response to challenge with methylated bovine serum albumin by 77 and 52% at the respective serum concentrations of 9 and 3 μM (850 and 250 mg/kg/day s.c., respectively) in a delayed-type hypersensitivity test in mice, and was effective in inhibiting ear swelling in a croton oil-induced dermatitis test in mice, giving 62 and 48% inhibition at 4 and 2 μM (250 and 64 mg/kg/day), respectively. Other specifically claimed diaminopropionic acid derivatives are:



Compound	R1	R2	R3	Formula
289033	Cl	Me	3,5-(OH)2-Ph	C ₂₆ H ₂₄ ClN ₃ O ₈
289034	Cl	Cl	3,5-(F)2-Ph	C ₂₅ H ₁₉ Cl ₂ F ₂ N ₃ O ₆
289035	Cl	Cl	3,5-(OH)2-Ph	C ₂₅ H ₂₁ Cl ₂ N ₃ O ₈
289036	Cl	H	3-OH-Ph	C ₂₅ H ₂₂ ClN ₃ O ₇
289037	Cl	H	3,5-(OH)2-Ph	C ₂₅ H ₂₂ ClN ₃ O ₈
289038	Cl	Cl	3-OH-Ph	C ₂₅ H ₂₁ Cl ₂ N ₃ O ₇
289039	Cl	Me	2-thienyl	C ₂₄ H ₂₂ ClN ₃ O ₆ S
289040	Cl	Cl	2-thienyl	C ₂₃ H ₁₉ Cl ₂ N ₃ O ₆ S
289041	Cl	Cl	3-thienyl	C ₂₃ H ₁₉ Cl ₂ N ₃ O ₆ S
289042	Cl	Me	3-thienyl	C ₂₄ H ₂₂ ClN ₃ O ₆ S
289043	Me	Me	2-thienyl	C ₂₅ H ₂₅ N ₃ O ₆ S
289044	Me	Me	3-thienyl	C ₂₅ H ₂₅ N ₃ O ₆ S

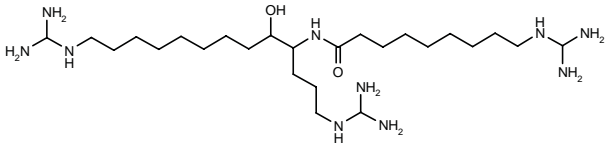
SOURCE – Roche.

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289440

9-(Diaminomethylamino)-*N*-[10-(diaminomethylamino)-1-[3-(diaminomethylamino)propyl]-2-hydroxydecyl]non-anamide



C25 H60 N10 O2; Mol wt: 532.8170

ACTION – Nitric oxide (NO) production inhibitor isolated from *Streptomyces* sp. POL-1142 (FERM P-15678), expected to be useful for the treatment or prevention of NO-mediated diseases, particularly myocardial infarction.

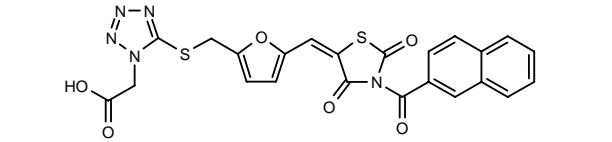
SOURCE – Pola Chemical.

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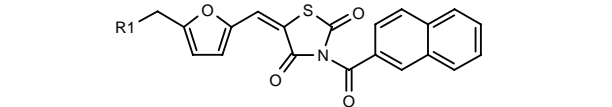
289493

2-[5-[5-[3-(2-Naphthylcarbonyl)-2,4-dioxothiazolidin-5-ylidenemethyl]furan-2-ylmethylsulfanyl]-1*H*-tetrazol-1-yl]acetic acid



C23 H15 N5 O6 S2; Mol wt: 521.5325

ACTION – A selective inhibitor of chymase, as demonstrated by an IC₅₀ value of 40.7 nM against enzyme from rhesus monkey heart versus IC₅₀ values > 1000 nM against bovine chymotrypsin and human cathepsin G. It is expected to be useful for the treatment of hypertension, cardiac hypertrophy, myocardial infarction, arteriosclerosis and diabetic or nondiabetic nephropathy. Other exemplified compounds from this series of *N*-substituted thiazolidine derivatives include the following:



Compound	R1	Formula
289494	1-Ph-5-tetrazolyl-S	C ₂₇ H ₁₇ N ₅ O ₄ S ₂
289496	H	C ₂₀ H ₁₃ NO ₄ S
289503	SAc	C ₂₂ H ₁₅ NO ₅ S ₂
289504	1-(CH ₂ CO ₂ Na)-5-tetrazolyl-S	C ₂₃ H ₁₄ N ₅ NaO ₆ S ₂

SOURCE – Toa Eiyo.

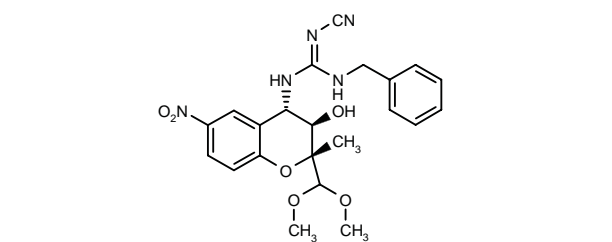
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KR-31372

287788

N-Benzyl-*N*''-cyano-*N*'-[2(*R*)-(dimethoxymethyl)-3(*R*)-hydroxy-2-methyl-6-nitro-3,4-dihydro-2*H*-1-benzopyran-4(*S*)-yl]guanidine



C22 H25 N5 O6; Mol wt: 455.4685

ACTION – Potassium channel opener proven to inhibit DNA synthesis and migration induced by oxidized LDL in cultured smooth muscle cells via activation of both Ca²⁺-activated and ATP-sensitive K⁺ channels. Compound also exerted antioxidant activity in human peritoneal mesothelial cells. *In vivo*, it exhibited strong antiangiogenic activity on neovascular formation in a rat sponge model of angiogenesis in comparison with other potassium channel openers such as lemakalim and BMS-180448. Potentially useful for the treatment of atherosclerosis.

SOURCES – Korea Research Institute of Chemical Technology, Taejon (KR); Pusan National University, Pusan (KR); Yonsei University, Seoul (KR).

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ANTIARRHYTHMIC DRUGS

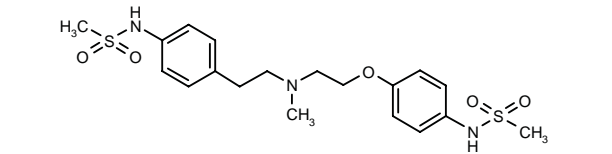
DOFETILIDE

Rec INN; BAN; USAN

138388

N-[4-[2-[*N*-[2-[4-(Methanesulfonamido)phenyl]ethyl]ethyl]-*N*-methylamino]ethoxy]phenyl]methanesulfonamide

UK-68798⁺



C19 H27 N3 O5 S2; Mol wt: 441.5720

Crystals, m.p. 147-9 °C.

ACTION – Antiarrhythmic agent with class III properties, a selective potassium channel blocker that blocks the cardiac ion channel carrying the rapid component of the delayed rectifier potassium current $K_{V(r)}$.

INDICATION – Maintenance of normal sinus rhythm in patients with atrial fibrillation/atrial flutter of greater than 1-week duration who have been converted to normal sinus rhythm, and conversion of atrial fibrillation and atrial flutter to normal sinus rhythm.

PRESENTATION – Capsules, 125, 250 and 500 mg.

PROPRIETARY NAME – Tikosyn (US).

SOURCE – Pfizer.

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36. Toivonen, L.K. et al. *Dofetilide is better tolerated than sotalol for the prevention of recurrence of atrial fibrillation and flutter*. PACE - Pacing Clin Electrophysiol 2000, 23(4, Part 2): Abst 382.

37. van Opstal, J.M. et al. *Azimilide and dofetilide produce similar electrophysiological and proarrhythmic effects in an animal model of acquired torsade de pointes arrhythmias*. PACE - Pacing Clin Electrophysiol 2000, 23(4, Part 2): Abst 714.

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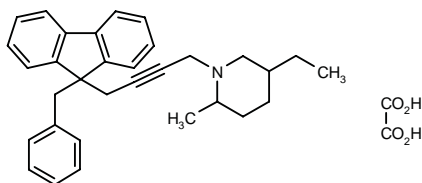
MONOGRAPH – Prous, J. and Castañer, J. *UK-68,798*. Drugs Fut 1991, 16(6): 0521.

*Drug Data Report 1990, 012(07): 0541.

UCL-1710

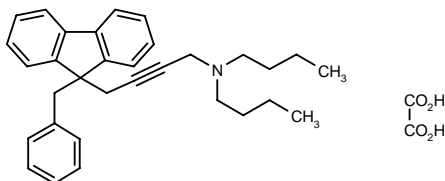
290061

1-[4-(9-Benzyl-9H-fluoren-9-yl)-2-butynyl]-5-ethyl-2-methylpiperidine oxalate



C32 H35 N . C2 H2 O4; Mol wt: 523.6693

ACTION – Potent and selective intermediate-conductance calcium-activated potassium (IK_{Ca}) channel blocker proven to inhibit in a concentration-dependent manner $^{86}Rb^+$ uptake into A23187-activated erythrocytes (IC_{50} = 2.9 μM). Compound was about 50-fold less potent than the reference IK_{Ca} blocker clotrimazole and exhibited a different mechanism of action, with a Hill coefficient of 2.0 versus 1.1 for clotrimazole. Potentially useful as an antiarrhythmic agent. Another cetiedil congener with IK_{Ca} -blocking activity is:



UCL-1994 [290064]: C32 H37 N . C2 H2 O4

SOURCE – University College London, London (GB).

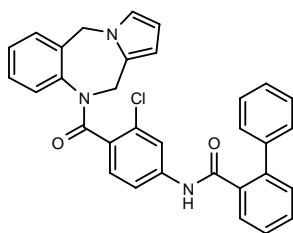
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HEART FAILURE THERAPY

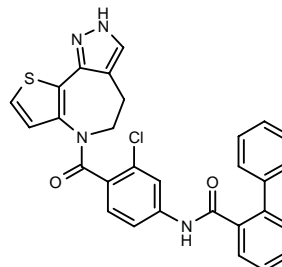
288876¹⁻⁶

N-[3-Chloro-4-(10,11-dihydro-5H-pyrrolo[2,1-*c*][1,4]benzodiazepin-10-ylcarbonyl)phenyl]biphenyl-2-carboxamide



C32 H24 Cl N3 O2; Mol wt: 518.0136

ACTION – Potent vasopressin (AVP) V_2 receptor antagonist (IC_{50} = 1.5 and 2.7 nM, respectively, for rat and human receptors) with good selectivity over V_{1a} receptors (IC_{50} = 16 and 370 nM, respectively, for rat and human receptors). *In vivo*, compound inhibited the antidiuretic action of AVP in water-loaded rats at doses of 3-10 mg/kg p.o. Potentially useful for normalizing plasma osmolality and controlling hyponatremia occurring in congestive heart failure, liver cirrhosis and renal failure. Another related compound is:



288878:⁶ C29 H21 Cl N4 O2 S

SOURCE – Wyeth-Ayerst.

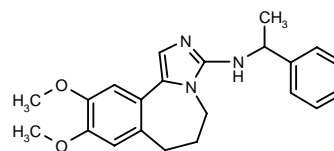
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3. Albright, J.D. et al. (American Cyanamid Co.) *Tricyclic benzazepine vasopressin antagonists*. US 5753648, WO 9749707.
4. Trybulski, E.J. et al. (American Home Products Corp.) *3-Carboxamide derivs. of 5H-pyrrolo[1,2-*c*][1,4]benzodiazepines*. US 5880122.
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6. Albright, J.D. et al. *The synthesis and vasopressin (AVP) antagonist activity of a novel series of *N*-aroyl-2,4,5,6-tetrahydropyrrolo[3,4-*d*]thieno[3,2-*b*]azepines*. Bioorg Med Chem Lett 2000, 10(8): 695.

289122

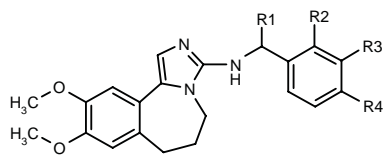
9,10-Dimethoxy-*N*-(1-phenylethyl)-6,7-dihydro-5H-imidazo[5,1-*a*][2]benzazepin-3-amine

N-(9,10-Dimethoxy-6,7-dihydro-5H-imidazo[5,1-*a*][2]benzazepin-3-yl)-*N*-(1-phenylethyl)amine



C22 H25 N3 O2; Mol wt: 363.4585

ACTION – Agent for the prevention or treatment of cardiovascular disorders such as congestive heart failure, hypotension, arrhythmia or cardiac reperfusion injury, and disorders related to cellular protein transport, for example osteoporosis, rheumatoid arthritis, allergy, restenosis, cancer, Kaposi's sarcoma, psoriasis and bacterial infections, as well as for treating or preventing nasal congestion and migraine. Other exemplified imidazo-benzazepine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
289123	Me	Br	H	F	C ₂₂ H ₂₃ BrFN ₃ O ₂
289124	Me	H	Me	Me	C ₂₄ H ₂₉ N ₃ O ₂
289125	vinyl	H	H	Cl	C ₂₃ H ₂₄ ClN ₃ O ₂
289128	CH(Me)Et	H	H	Cl	C ₂₅ H ₃₀ ClN ₃ O ₂
289129	i-Pr	H	H	N(Et)2	C ₂₈ H ₃₈ N ₄ O ₂
289130	CH(Me)Et	F	H	H	C ₂₅ H ₃₀ FN ₃ O ₂
289131	C6H13	H	Cl	Cl	C ₂₇ H ₃₃ Cl ₂ N ₃ O ₂

SOURCE – Procter & Gamble.

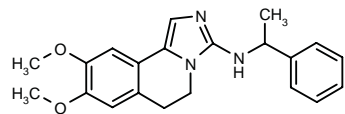
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289133

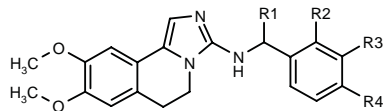
8,9-Dimethoxy-*N*-(1-phenylethyl)-5,6-dihydroimidazo[5,1-*a*]isoquinolin-3-amine

N-(8,9-Dimethoxy-5,6-dihydroimidazo[5,1-*a*]isoquinolin-3-yl)-*N*-(1-phenylethyl)amine



C21 H23 N3 O2; Mol wt: 349.4317

ACTION – Agent for the prevention or treatment of cardiovascular disorders such as congestive heart failure, hypotension, arrhythmia or cardiac reperfusion injury, and disorders related to cellular protein transport, for example osteoporosis, rheumatoid arthritis, allergy, restenosis, cancer, Kaposi’s sarcoma, psoriasis and bacterial infections, as well as for treating or preventing nasal congestion and migraine. Other exemplified imidazo-isoquinoline derivatives include the following:



Compound	R1	R2	R3	R4	Formula
289134	Me	Br	H	F	C ₂₁ H ₂₁ BrFN ₃ O ₂
289135	Me	H	Me	Me	C ₂₃ H ₂₇ N ₃ O ₂
289136	vinyl	H	H	Cl	C ₂₂ H ₂₂ ClN ₃ O ₂
289137	CH(Me)Et	H	H	Cl	C ₂₄ H ₂₈ ClN ₃ O ₂
289138	i-Pr	H	H	N(Et)2	C ₂₇ H ₃₆ N ₄ O ₂
289139	CH(Me)Et	F	H	H	C ₂₄ H ₂₈ FN ₃ O ₂
289140	C6H13	H	Cl	Cl	C ₂₆ H ₃₁ Cl ₂ N ₃ O ₂

SOURCE – Procter & Gamble.

REFERENCES

1. Liu, S. et al. (The Procter & Gamble Co.) *Imidazo-isoquinoline cpds., their compsns. and uses.* WO 0021961.

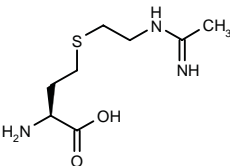
TREATMENT OF SHOCK

GW-274150*

269164

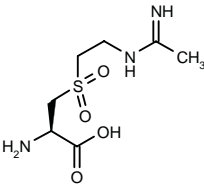
S-[2-(1-Iminoethylamino)ethyl]-*L*-homocysteine

2(*S*)-Amino-7-(1-iminoethylamino)-5-thiaheptanoic acid



C8 H17 N3 O2 S; Mol wt: 219.3073

ACTION – Potent inhibitor of the inducible form of nitric oxide synthase (iNOS; IC₅₀ = 1.4 μM against human enzyme) with good selectivity over endothelial and neuronal NOS isoforms (IC₅₀ = 466 and 145 μM, respectively). Potentially useful for the treatment of conditions including shock and various inflammatory processes. Another acetamidine derivative of hetero-substituted *L*-lysine is:



GW-273629 [288633]: C7 H15 N3 O4 S

SOURCE – Glaxo Wellcome.

REFERENCES

1. Beams, R.M. et al. (Glaxo Wellcome plc) *Nitric oxide synthase inhibitors.* EP 0958277, JP 2000504041, WO 9830537.

2. Young, R.J. et al. *Inhibition of inducible nitric oxide synthase by acetamidine derivatives of hetero-substituted lysine and homolysine.* Bioorg Med Chem Lett 2000, 10(6): 597.

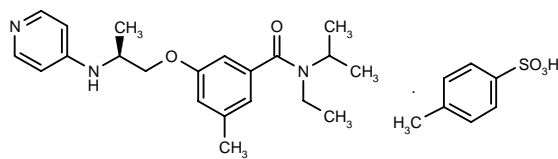
*Identified compound **269164** Drug Data Rep 1998, 020(11): 0980.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

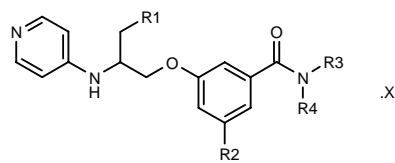
288669

N-Ethyl-N-isopropyl-3-methyl-5-[2(S)-(4-pyridylamino)-propoxy]benzamide 4-methylbenzenesulfonate



C21 H29 N3 O2 . C7 H8 O3 S; Mol wt: 527.6823

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of human thrombin (IC₅₀ < 1 nM). Compound was shown to extend the activated partial thromboplastin time (APTT) of human plasma by 1.5 times at 40 nM. Other specifically claimed compounds from this series of benzamide derivatives are:



Compound	R1	R2	R3	R4	X	Isomer	Formula
288670	H	Me	i-Pr	i-Pr		S	C ₂₂ H ₃₁ N ₃ O ₂
288671	H	Me	Me	i-Pr		S	C ₂₀ H ₂₇ N ₃ O ₂
288672	H	Me	Me	Pr		S	C ₂₀ H ₂₇ N ₃ O ₂
288673	H	Me	Pr	Pr		S	C ₂₂ H ₃₁ N ₃ O ₂
288674	H	Me	Pr	Et		S	C ₂₁ H ₂₉ N ₃ O ₂
288675	H	Me	Bu	Pr		S	C ₂₃ H ₃₃ N ₃ O ₂
288676	H	Me	i-Pr	cyclohexyl		S	C ₂₅ H ₃₅ N ₃ O ₂
288677	H	Me	Pr	i-Pr		S	C ₂₂ H ₃₁ N ₃ O ₂
288678	H	Cl	Pr	i-Pr		S	C ₂₁ H ₂₈ ClN ₃ O ₂
288679	Me	Cl	i-Pr	i-Pr	HCl		C ₂₂ H ₃₀ ClN ₃ O ₂ .HCl

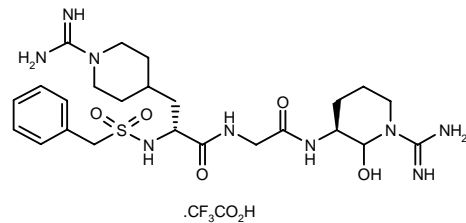
SOURCE – Glaxo Wellcome.

REFERENCES

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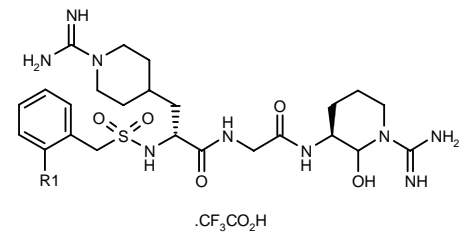
288887

N-(Benzylsulfonyl)-3-(1-amidino-4-piperidiny)-D-alanyl-glycine [1-amidino-2-hydroxypiperidin-3(S)-yl]amide tri-fluoroacetate



C24 H39 N9 O5 S . C2 H F3 O2; Mol wt: 679.7180

ACTION – Anticoagulant, an inhibitor of factor Xa (IC₅₀ = 0.83 nM) with high selectivity relative to other trypsin-like serine proteases including plasmin, trypsin and thrombin (IC₅₀ = 869, 169 and > 2,500 nM, respectively). Other guanylpiperidine peptidomimetics are:



Compound	R1	Formula
288888	CO2Me	C ₂₈ H ₄₁ N ₉ O ₇ S.C ₂ HF ₃ O ₂
288889	CO2H	C ₂₈ H ₃₉ N ₉ O ₇ S.C ₂ HF ₃ O ₂
288890	5-tetrazolyl	C ₂₅ H ₃₈ N ₁₃ O ₅ S.C ₂ HF ₃ O ₂

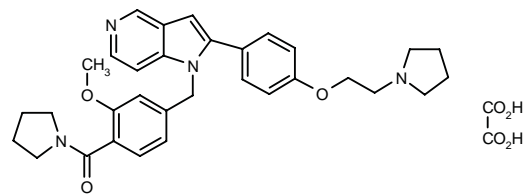
SOURCE – Corvas.

REFERENCES

1. Tamura, S.Y. et al. *Guanylpiperidine peptidomimetics: Potent and selective bis-cation inhibitors of factor Xa*. Bioorg Med Chem Lett 2000, 10(8): 745.

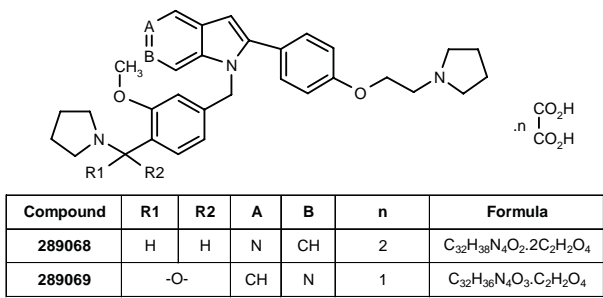
289067

1-[2-Methoxy-4-[2-[4-[2-(pyrrolidin-1-yl)ethoxy]phenyl]-1H-pyrrolo[3,2-c]pyridin-1-ylmethyl]phenyl]-1-(pyrrolidin-1-yl)methanone oxalate



C32 H36 N4 O3 . C2 H2 O4; Mol wt: 614.6952

ACTION – Anticoagulant, a potent thrombin inhibitor with high oral availability and favorable pharmacokinetics following oral administration. Other exemplified azaindole derivatives are:



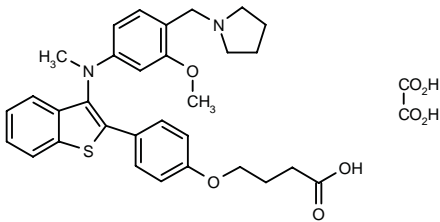
SOURCE – Lilly.

REFERENCES

1. Bastian, J.A. et al. (Eli Lilly and Company) *Azaindole derivs. and their use as antithrombotic agents*. EP 0997465, JP 2000143663.

289099

4-[4-[3-[N-[3-Methoxy-4-(1-pyrrolidinylmethyl)phenyl]-N-methylamino]-1-benzothien-2-yl]phenoxy]butyric acid oxalate



C31 H34 N2 O4 S . C2 H2 O4; Mol wt: 620.7194

ACTION – A representative compound from a series of benzothiophene derivatives with potent thrombin-inhibitory activity, high oral availability and favorable pharmacokinetics following oral administration.

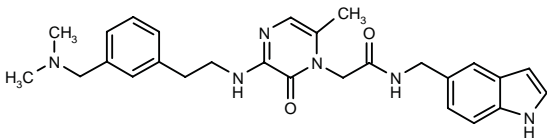
SOURCE – Lilly.

REFERENCES

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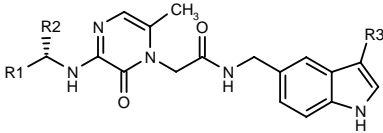
289103

2-[3-[2-[3-(Dimethylaminomethyl)phenyl]ethylamino]-6-methyl-2-oxo-1,2-dihydropyrazin-1-yl]-N-(1*H*-indol-5-ylmethyl)acetamide



C27 H32 N6 O2; Mol wt: 472.5898

ACTION – Antithrombotic agent, a potent and selective thrombin inhibitor with good oral bioavailability. Other compounds from this class of nonbasic or weakly basic bicyclic heterocyclic arginine mimics include the following:



Compound	R1	R2	R3	Formula
289105	CH2Ph	CH2N(Me)2	H	C ₂₇ H ₃₂ N ₆ O ₂
289107	H	3-(MeNH)-PhCH2	Me	C ₂₆ H ₃₀ N ₆ O ₂
289109	H	3-(MeOCH2CH2NHCH2)-PhCH2	Me	C ₂₉ H ₃₆ N ₆ O ₃
289112	H	1-(cyclopropyl-CH2)-2(R)-pyrrolidinyl	Me	C ₂₈ H ₃₈ N ₆ O ₂
289118	H	1-cyclopentyl-2(R)-pyrrolidinyl	Me	C ₂₇ H ₃₆ N ₆ O ₂
289119	H	1- <i>i</i> -Bu-2(R)-pyrrolidinyl	Me	C ₂₆ H ₃₆ N ₆ O ₂

SOURCE – Pfizer.

REFERENCES

1. Blagg, J. et al. (Pfizer Inc.;Pfizer Ltd.) *Antithrombotic agents*. EP 0997474.

289732

Conformation-specific murine anti-human von Willebrand factor antibody

ACTION – Conformation-specific anti-human von Willebrand factor (vWF) antibody, a recombinantly produced single-chain variable region immunoglobulin (ScFv) fragment that selectively binds to activated vWF, thereby inhibiting its interaction with platelets. The antibody does not bind to the circulating unactivated form of vWF, resulting in a safer and more efficacious anti-thrombotic agent.

SOURCE – Brigham & Women’s Hospital, Boston, MA (US).

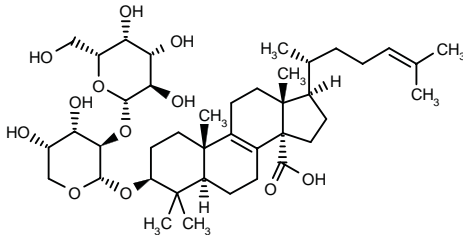
REFERENCES

1. Handin, R.I. et al. (Brigham & Women’s Hospital) *Conformation-specific anti-Von Willebrand factor antibodies*. WO 0024781.

ERYLOSIDE F

288492

3β-O-[2-O-(β-D-Galactopyranosyl)-α-L-arabino-pyranosyloxy]-4,4-dimethylcholesta-8(9),24-diene-14α-carboxylic acid



C41 H66 O12; Mol wt: 750.9604

ACTION – Thrombin receptor antagonist, a steroidal disaccharide metabolite extracted from the marine sponge *Erylus formosus*. Compound was able to inhibit platelet aggregation induced by the thrombin receptor-activating peptide SFLLRN and by the TxA₂ mimetic U-46619 (IC₅₀ = 0.3 and 1.7 µg/ml, respectively). The potency of compound against thrombin-induced platelet aggregation was approximately 20-fold lower than against SFLLRN-induced aggregation.

SOURCES – Glaxo Wellcome; Harbor Branch Oceanographic Institution.

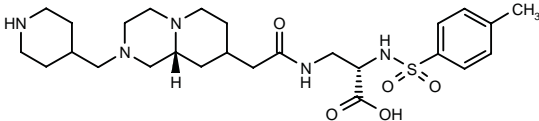
REFERENCES

1. Stead, P. et al. *Eryloside F, a novel penasterol disaccharide possessing potent thrombin receptor antagonist activity*. Bioorg Med Chem Lett 2000, 10(7): 661.

ANTIPLATELET THERAPY

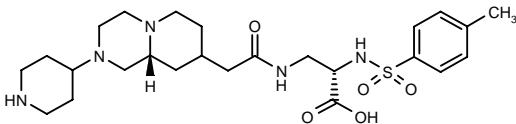
289173

2(S)-(4-Methylphenylsulfonamido)-3-[2-[(9a*R*)-2-(4-piperidinylmethyl)perhydro-2*H*-pyrido[1,2-*a*]pyrazin-8-yl]acetamido]propionic acid



C26 H41 N5 O5 S; Mol wt: 535.7059

ACTION – Cell adhesion inhibitor shown to potently inhibit aggregation induced by ADP in guinea pig platelet-rich plasma (PRP; IC₅₀ = 33 nM). Another compound from this series of octahydropyrido[1,2-*a*]pyrazine derivatives is:



289174: C25 H39 N5 O5 S

SOURCE – Takeda.

REFERENCES

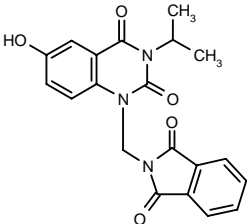
1. Tamura, N. et al. (Takeda Chemical Industries, Ltd.) *Octahydropyrido[1,2-a]pyrazine derivs*. JP 2000086659.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

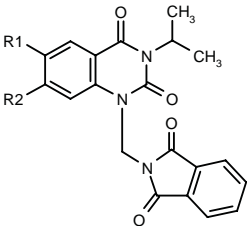
288527

6-Hydroxy-3-isopropyl-1-(phthalimidomethyl)-1,2,3,4-tetrahydroquinazoline-2,4-dione



C20 H17 N3 O5; Mol wt: 379.3703

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor for the treatment of benign prostatic hypertrophy, urinary incontinence, male and female sexual dysfunction, pulmonary hypertension, stroke, atherosclerosis, as well as asthma, bronchitis, allergic rhinitis, glaucoma and gastrointestinal motility disorders. Other specifically claimed quinazolidinedione derivatives include the following:



Compound	R1	R2	Formula
288533	H	H	C ₂₀ H ₁₇ N ₃ O ₄
288534	OMe	OMe	C ₂₂ H ₂₁ N ₃ O ₆
288535	NO2	H	C ₂₀ H ₁₆ N ₄ O ₆
288536	H	Cl	C ₂₀ H ₁₆ ClN ₃ O ₄

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Bovy, P.R. et al. (Sanofi-Synthélabo) *Quinazolidinedione derivs., preparation and therapeutic uses*. WO 0020412.

ACTION – Thrombin receptor antagonist, a steroidal disaccharide metabolite extracted from the marine sponge *Erylus formosus*. Compound was able to inhibit platelet aggregation induced by the thrombin receptor-activating peptide SFLLRN and by the TxA₂ mimetic U-46619 (IC₅₀ = 0.3 and 1.7 µg/ml, respectively). The potency of compound against thrombin-induced platelet aggregation was approximately 20-fold lower than against SFLLRN-induced aggregation.

SOURCES – Glaxo Wellcome; Harbor Branch Oceanographic Institution.

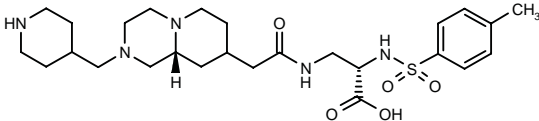
REFERENCES

1. Stead, P. et al. *Eryloside F, a novel penasterol disaccharide possessing potent thrombin receptor antagonist activity*. Bioorg Med Chem Lett 2000, 10(7): 661.

ANTIPLATELET THERAPY

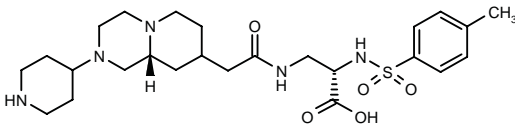
289173

2(S)-(4-Methylphenylsulfonamido)-3-[2-[(9a*R*)-2-(4-piperidinylmethyl)perhydro-2*H*-pyrido[1,2-*a*]pyrazin-8-yl]acetamido]propionic acid



C26 H41 N5 O5 S; Mol wt: 535.7059

ACTION – Cell adhesion inhibitor shown to potently inhibit aggregation induced by ADP in guinea pig platelet-rich plasma (PRP; IC₅₀ = 33 nM). Another compound from this series of octahydropyrido[1,2-*a*]pyrazine derivatives is:



289174: C25 H39 N5 O5 S

SOURCE – Takeda.

REFERENCES

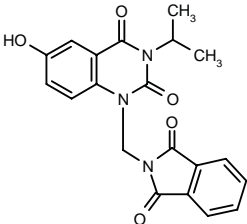
1. Tamura, N. et al. (Takeda Chemical Industries, Ltd.) *Octahydropyrido[1,2-*a*]pyrazine derivs.* JP 2000086659.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

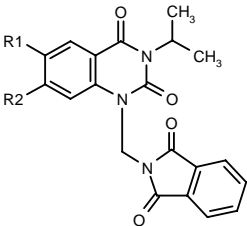
288527

6-Hydroxy-3-isopropyl-1-(phthalimidomethyl)-1,2,3,4-tetrahydroquinazoline-2,4-dione



C20 H17 N3 O5; Mol wt: 379.3703

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor for the treatment of benign prostatic hypertrophy, urinary incontinence, male and female sexual dysfunction, pulmonary hypertension, stroke, atherosclerosis, as well as asthma, bronchitis, allergic rhinitis, glaucoma and gastrointestinal motility disorders. Other specifically claimed quinazolidinedione derivatives include the following:



Compound	R1	R2	Formula
288533	H	H	C ₂₀ H ₁₇ N ₃ O ₄
288534	OMe	OMe	C ₂₂ H ₂₁ N ₃ O ₆
288535	NO2	H	C ₂₀ H ₁₆ N ₄ O ₆
288536	H	Cl	C ₂₀ H ₁₆ ClN ₃ O ₄

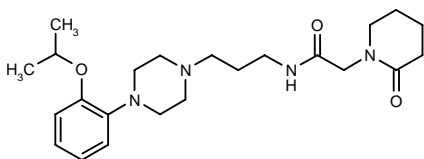
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Bovy, P.R. et al. (Sanofi-Synthélabo) *Quinazolidinedione derivs., preparation and therapeutic uses*. WO 0020412.

289882

N-[3-[4-[2-(Isopropoxy)phenyl]-1-piperazinyl]propyl]-2-oxopiperidine-1-acetamide



C23 H36 N4 O3; Mol wt: 416.5624

ACTION – Potent and selective α_1 -adrenoceptor antagonist that binds with high affinity to human α_{1A} -adrenoceptors ($K_i = 0.66$ nM) and shows high selectivity over α_{1B} - and α_{1D} -adrenoceptors ($K_i = 10,000$ and 80 nM, respectively). Potentially useful for the treatment of benign prostatic hyperplasia.

SOURCE – R.W. Johnson.

REFERENCES

1. Jolliffe, L. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Arylsbstd. piperazines useful in the treatment of benign prostatic hyperplasia*. EP 0984777, US 6071915, WO 9851298.
2. Li, X. et al. *Novel arylpiperazines as selective α_1 -adrenergic receptor antagonists*. Bioorg Med Chem Lett 2000, 10(10): 1093.

p-TIA**288873**

H-L-Phe-L-Asn-L-Trp-L-Arg-L-Cys-L-Cys-L-Leu-L-Ile-L-Pro-L-Ala-L-Cys-L-Arg-L-Arg-L-L-Asn-L-His-L-Lys-L-Lys-L-Phe-L-Cys-OH

C105 H163 N35 O22 S4; Mol wt: 2395.9300

ACTION – A representative peptide from a novel class of conotoxins named p-conotoxins, isolated from cone snails, with selective α_1 -adrenoceptor-antagonist activity. In binding assays, compound exhibited respective $-\log K_i$ values of 7.29 ± 0.141 , 7.70 ± 0.179 and 7.09 ± 0.057 for rat α_{1A} -, hamster α_{1B} - and rat α_{1D} -adrenoceptors cloned in COS-1 cells. Potentially useful for treating prostatic hyperplasia, arrhythmias, hypertension or coronary heart failure, craving or chronic pain, neuropathic pain or inflammatory pain.

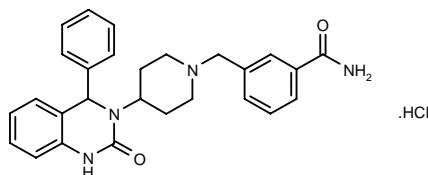
SOURCE – University of Queensland, Queensland (AU).

REFERENCES

1. Lewis, R.J. et al. (University of Queensland) *Novel peptides*. WO 0020443.

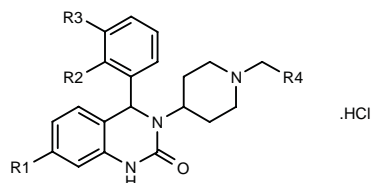
TREATMENT OF URINARY INCONTINENCE**289466**

3-[4-(2-Oxo-4-phenyl-1,2,3,4-tetrahydroquinazolin-3-yl)piperidin-1-ylmethyl]benzamide hydrochloride



C27 H28 N4 O2 . HCl; Mol wt: 477.0051

ACTION – Agent for the treatment of urinary incontinence, a selective muscarinic M_3 receptor antagonist, as demonstrated by pA_2 values of 8.58, 7.37 and 6.71 when tested *in vitro* for its ability to inhibit acetylcholine-, McN-A-343- and carbachol-induced contractions in guinea pig urinary bladder, rabbit vas deferens and guinea pig atrium preparations, respectively. Other exemplified compounds from this series of quinazolinone derivatives include the following:



Compound	R1	R2	R3	R4	Formula
289467	H	H	H	3-(MeOCH2)-Ph	C ₂₈ H ₃₂ ClN ₃ O ₂
289469	H	H	H	3-cyclohexenyl	C ₂₆ H ₃₂ ClN ₃ O
289471	H	F	H	Ph	C ₂₆ H ₂₇ ClFN ₃ O
289472	H	H	OMe	Ph	C ₂₇ H ₃₀ ClN ₃ O ₂
289473	Cl	H	H	Ph	C ₂₆ H ₂₇ Cl ₂ N ₃ O

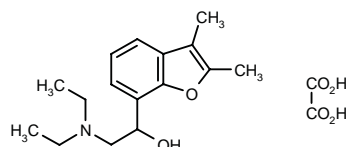
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Muraoka, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Quinazolinone derivs*. WO 0023436.

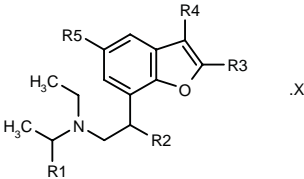
289676

2-(Diethylamino)-1-(2,3-dimethylbenzofuran-7-yl)-1-ethanol hemioxalate



C16 H23 N O2 . C2 H2 O4; Mol wt: 351.3965

ACTION – α -Adrenoceptor ligand with no effect on β -adrenoceptors, exhibiting selective contractile activity for urethral over arterial smooth muscle and, in addition, venoconstrictive activity. Potentially useful for the treatment of urinary incontinence, venous insufficiency and venous ulcers. Other compounds from this series of 2-aminoethylbenzofuran derivatives include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
289678	H	OH	Ph	Ph	H		C ₂₆ H ₂₇ NO ₂
289679	H	OH	Me	Me	Me		C ₁₇ H ₂₅ NO ₂
289680	H	OH	Pr	Me	H	HCl	C ₁₈ H ₂₇ NO ₂ ·HCl
289681	H	OH	Me	Me	H	HCl	C ₁₆ H ₂₃ NO ₂ ·HCl
289682	Me	OH	Me	Me	H	oxalate	C ₁₇ H ₂₅ NO ₂ ·C ₂ H ₂ O ₄
289683	H	H	Et	Et	H		C ₁₈ H ₂₇ NO
289685	H	OH	CHF2	Me	H		C ₁₆ H ₂₁ F ₂ NO ₂

SOURCE – Sanofi-Synthélabo.

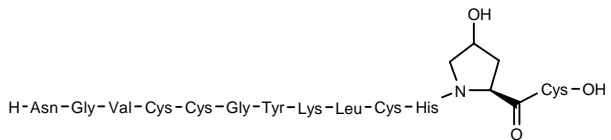
REFERENCES

1. Philippo, C. et al. (Sanofi-Synthélabo) *2-Aminoethyl-benzofuran derivs., preparation thereof and therapeutical use thereof*. JP 2000506157, US 6063810, WO 9732870.

χ -MrIA

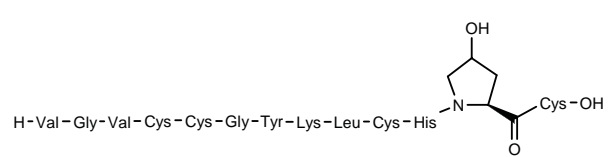
288875

L-Asparaginyl-glycyl-L-valyl-L-cysteinyl-L-cysteinyl-glycyl-L-tyrosyl-L-lysyl-L-leucyl-L-cysteinyl-L-histidyl-L-(4-hydroxy)prolyl-L-cysteine



C57 H89 N17 O17 S4; Mol wt: 1412.6960

ACTION – Peptide isolated from the venom of the mollusk *Conus marmoreus* belonging to a new class of conotoxins, designated χ -conotoxins, which differ from other conotoxins in their ability to selectively inhibit neuronal amine transporters such as the noradrenaline transporter; all other conotoxin peptides reported to date target ion channels or receptors on cell surfaces. *In vitro*, compound inhibited [³H]-noradrenaline uptake into CHO cells expressing the human neuronal noradrenaline transporter with an IC₅₀ of about 7 nM, and it was shown to be devoid of anticholinergic effects, sodium channel-blocking activity and dopamine transporter-inhibitory activity. The compound is expected to be useful for the treatment of urinary and fecal incontinence, cardiovascular disease such as arrhythmia or coronary heart failure, mood disorders and pain. Another exemplified peptide is:



χ -MrIB [288877]: C58 H92 N16 O16 S4

SOURCE – University of Queensland, Queensland (AU).

REFERENCES

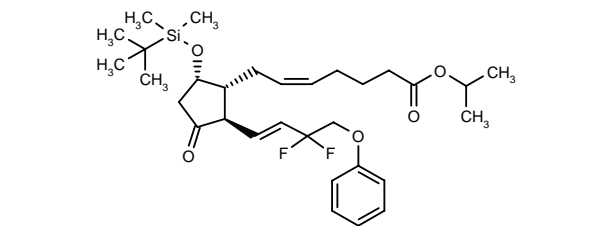
1. Lewis, R.J. et al. (University of Queensland) *Novel peptides*. WO 0020444.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

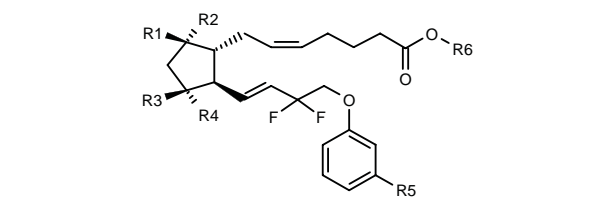
288934

9-*O*-(*tert*-Butyldimethylsilyl)-15-deoxy-15,15-difluoro-16-phenoxy-17,18,19,20-tetranorprostaglandin D₂ isopropyl ester



C31 H46 F2 O5 Si; Mol wt: 564.7814

ACTION – Prostaglandin derivative for the treatment of gastric ulcer, osteoporosis, neuronal inflammation, pain and allergy, as well as for inducing labor or for the improvement of blood flow. Other exemplified compounds are:



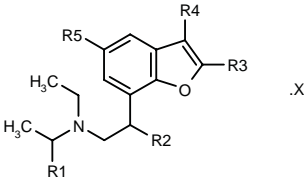
Compound	R1	R2	R3	R4	R5	R6	Formula
288935	H	OH		-O-	Cl	i-Pr	C ₂₅ H ₃₁ ClF ₂ O ₅
288936		-O-	H	2-THP-O	H	H	C ₂₇ H ₃₄ F ₂ O ₆
288938		-O-	H	OH	H	i-Pr	C ₂₆ H ₃₂ F ₂ O ₅
288939		-O-	H	H	H	H	C ₂₂ H ₂₆ F ₂ O ₄

SOURCE – Asahi Glass.

REFERENCES

1. Matsumura, Y. and Mori, N. (Asahi Glass Co., Ltd.) *15-Deoxy-15,15-difluoro-prostaglandin derivs. and their salts*. JP 2000080075.

ACTION – α -Adrenoceptor ligand with no effect on β -adrenoceptors, exhibiting selective contractile activity for urethral over arterial smooth muscle and, in addition, venoconstrictive activity. Potentially useful for the treatment of urinary incontinence, venous insufficiency and venous ulcers. Other compounds from this series of 2-aminoethylbenzofuran derivatives include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
289678	H	OH	Ph	Ph	H		C ₂₆ H ₂₇ NO ₂
289679	H	OH	Me	Me	Me		C ₁₇ H ₂₅ NO ₂
289680	H	OH	Pr	Me	H	HCl	C ₁₈ H ₂₇ NO ₂ ·HCl
289681	H	OH	Me	Me	H	HCl	C ₁₆ H ₂₃ NO ₂ ·HCl
289682	Me	OH	Me	Me	H	oxalate	C ₁₇ H ₂₅ NO ₂ ·C ₂ H ₂ O ₄
289683	H	H	Et	Et	H		C ₁₈ H ₂₇ NO
289685	H	OH	CHF2	Me	H		C ₁₆ H ₂₁ F ₂ NO ₂

SOURCE – Sanofi-Synthélabo.

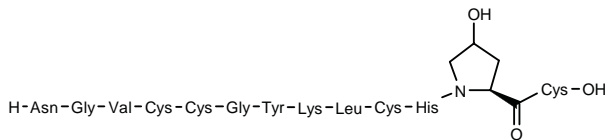
REFERENCES

1. Philippo, C. et al. (Sanofi-Synthélabo) *2-Aminoethyl-benzofuran derivs., preparation thereof and therapeutical use thereof*. JP 2000506157, US 6063810, WO 9732870.

χ -MrIA

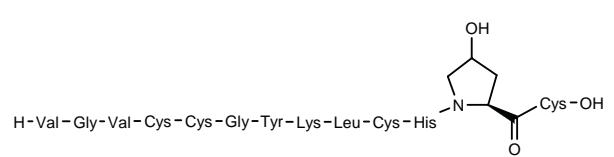
288875

L-Asparaginyl-glycyl-L-valyl-L-cysteinyl-L-cysteinyl-glycyl-L-tyrosyl-L-lysyl-L-leucyl-L-cysteinyl-L-histidyl-L-(4-hydroxy)prolyl-L-cysteine



C57 H89 N17 O17 S4; Mol wt: 1412.6960

ACTION – Peptide isolated from the venom of the mollusk *Conus marmoreus* belonging to a new class of conotoxins, designated χ -conotoxins, which differ from other conotoxins in their ability to selectively inhibit neuronal amine transporters such as the noradrenaline transporter; all other conotoxin peptides reported to date target ion channels or receptors on cell surfaces. *In vitro*, compound inhibited [³H]-noradrenaline uptake into CHO cells expressing the human neuronal noradrenaline transporter with an IC₅₀ of about 7 nM, and it was shown to be devoid of anticholinergic effects, sodium channel-blocking activity and dopamine transporter-inhibitory activity. The compound is expected to be useful for the treatment of urinary and fecal incontinence, cardiovascular disease such as arrhythmia or coronary heart failure, mood disorders and pain. Another exemplified peptide is:



χ -MrIB [288877]: C58 H92 N16 O16 S4

SOURCE – University of Queensland, Queensland (AU).

REFERENCES

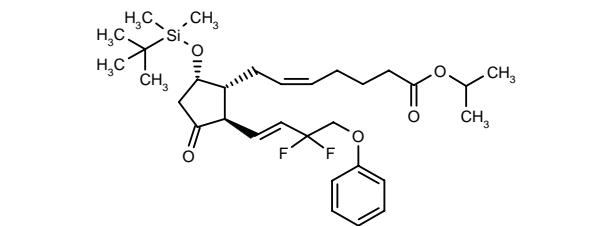
1. Lewis, R.J. et al. (University of Queensland) *Novel peptides*. WO 0020444.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

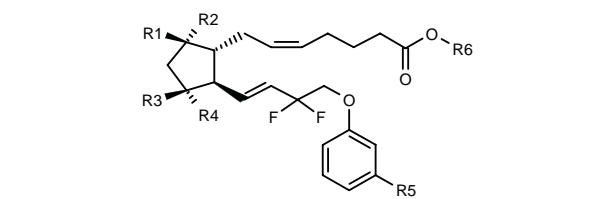
288934

9-*O*-(*tert*-Butyldimethylsilyl)-15-deoxy-15,15-difluoro-16-phenoxy-17,18,19,20-tetranorprostaglandin D₂ isopropyl ester



C31 H46 F2 O5 Si; Mol wt: 564.7814

ACTION – Prostaglandin derivative for the treatment of gastric ulcer, osteoporosis, neuronal inflammation, pain and allergy, as well as for inducing labor or for the improvement of blood flow. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
288935	H	OH		-O-	Cl	i-Pr	C ₂₅ H ₃₁ ClF ₂ O ₅
288936		-O-	H	2-THP-O	H	H	C ₂₇ H ₃₄ F ₂ O ₆
288938		-O-	H	OH	H	i-Pr	C ₂₆ H ₃₂ F ₂ O ₅
288939		-O-	H	H	H	H	C ₂₂ H ₂₆ F ₂ O ₄

SOURCE – Asahi Glass.

REFERENCES

1. Matsumura, Y. and Mori, N. (Asahi Glass Co., Ltd.) *15-Deoxy-15,15-difluoro-prostaglandin derivs. and their salts*. JP 2000080075.

289308

Polypeptide corresponding to amino acids 254-323 of a 95-kD protein isolated from the outer membrane of *Helicobacter pylori*

ACTION – Fragment of an outer membrane protein isolated from *Helicobater pylori*, found to protect mice against *H. pylori* infection. Vaccine compositions comprising an effective amount of this protein, or antibodies to this protein, are claimed to actively or passively immunize against *H. pylori* infection.

SOURCE – Chiron Behring.

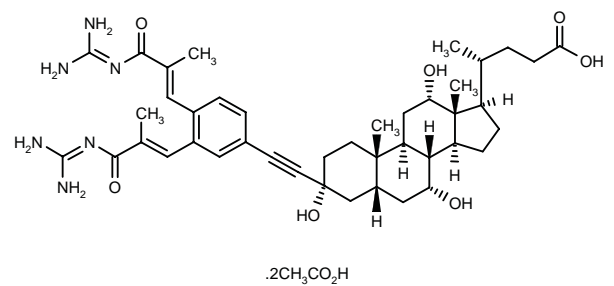
REFERENCES

1. Knapp, B. et al. (Chiron Behring GmbH & Co.) *Helicobacter pylori* vaccine. DE 19847628, WO 0022135.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

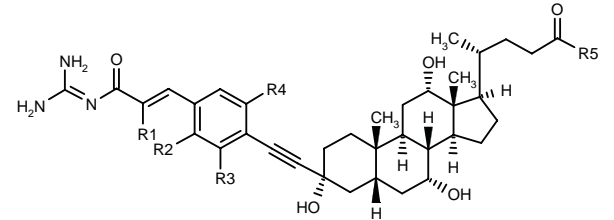
289495

3β-[3,4-Bis[3-guanidino-2-methyl-3-oxo-1(*E*)-propenyl]-phenylethynyl]-3α,7α,12α-trihydroxy-5β-cholan-24-oic acid



C42 H58 N6 O7 . 2 C2 H4 O2; Mol wt: 879.0584

ACTION – Agent for the prophylaxis or treatment of gallstones that acts by inhibiting the Na⁺/H⁺ exchanger subtype 3 (NHE3), as demonstrated in LAP1 cells expressing the human NHE3 (IC₅₀ = 1.7 μM). Other compounds from this series of bile acid-substituted phenyl alkenoyl guanidines include the following:



Compound	R1	R2	R3	R4	R5	Formula
289497	Me	CH=C(Me)CO-N=C(NH2)2	H	H	OCH2Ph	C ₄₉ H ₆₄ N ₆ O ₇
289498	H	H	H	H	OCH2Ph	C ₄₃ H ₅₆ N ₃ O ₆
289499	H	H	H	H	OMe	C ₃₇ H ₅₁ N ₃ O ₆
289500	Me	CH=C(Me)CO-N=C(NH2)2	H	H	NHCH2CO2H	C ₄₄ H ₆₁ N ₇ O ₈
289501	Me	H	F	H	OH	C ₃₇ H ₅₀ FN ₃ O ₆
289502	Me	H	F	F	OH	C ₃₇ H ₄₉ F ₂ N ₃ O ₆

SOURCE – Aventis Pharma.

REFERENCES

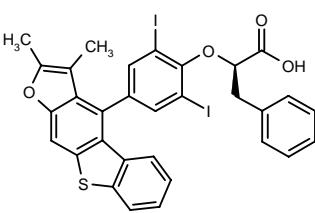
1. Weichert, A. et al. (Aventis Pharma Deutschland GmbH) *Bile-acid subst. phenyl alkenoyl guanidines, method for the production thereof, use thereof as medicaments or diagnostic agents and medicaments that contain them.* DE 19849722, WO 0024761.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

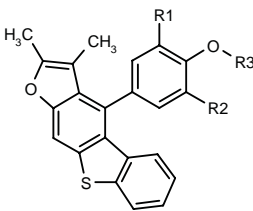
289087

2(*R*)-[4-(2,3-Dimethyl[1]benzothieno[3,2-*f*]benzofuran-4-yl)-2,6-diiodophenoxy]-3-phenylpropionic acid



C31 H22 I2 O4 S; Mol wt: 744.3768

ACTION – Protein-tyrosine-phosphatase (PTP) inhibitor found to inhibit rat hepatic microsomal PTP activity by 72.70% at 50 μM using triphosphorylated insulin receptor dodecaphosphopeptide as substrate and to give an IC₅₀ value of 0.074 μM when tested for inhibition of human recombinant PTP1B *in vitro*. In diabetic *ob/ob* mice, it lowered plasma glucose and insulin levels by 43 and 39% from controls, respectively. The compound is potentially useful for the treatment of insulin resistance associated with obesity, diabetes mellitus, glucose intolerance, hypertension and ischemic diseases of the large and small blood vessels. Other specifically claimed 4-aryl-1-oxa-9-thia-cyclopenta[*b*]fluorenes are:



Compound	R1	R2	R3	Formula
289089	H	H	Me	C ₂₃ H ₁₈ O ₂ S
289090	H	H	H	C ₂₂ H ₁₆ O ₂ S
289091	I	I	H	C ₂₂ H ₁₄ I ₂ O ₂ S
289094	I	I	(<i>R</i>)-CH(Me)CO2H	C ₂₅ H ₁₈ I ₂ O ₄ S

SOURCE – American Home Products.

REFERENCES

1. Wrobel, J.E. and Li, Z. (American Home Products Corp.) *4-Aryl-1-oxa-9-thia-cyclopenta[b]fluorenes.* US 6057316.

289308

Polypeptide corresponding to amino acids 254-323 of a 95-kD protein isolated from the outer membrane of *Helicobacter pylori*

ACTION – Fragment of an outer membrane protein isolated from *Helicobater pylori*, found to protect mice against *H. pylori* infection. Vaccine compositions comprising an effective amount of this protein, or antibodies to this protein, are claimed to actively or passively immunize against *H. pylori* infection.

SOURCE – Chiron Behring.

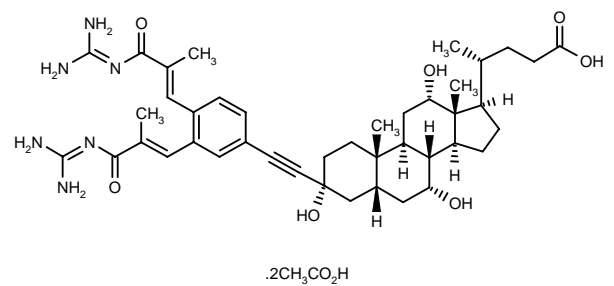
REFERENCES

1. Knapp, B. et al. (Chiron Behring GmbH & Co.) *Helicobacter pylori* vaccine. DE 19847628, WO 0022135.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

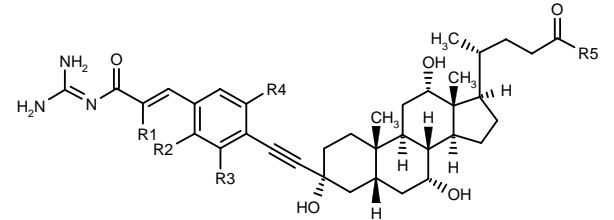
289495

3β-[3,4-Bis[3-guanidino-2-methyl-3-oxo-1(*E*)-propenyl]-phenylethynyl]-3α,7α,12α-trihydroxy-5β-cholan-24-oic acid



C42 H58 N6 O7 . 2 C2 H4 O2; Mol wt: 879.0584

ACTION – Agent for the prophylaxis or treatment of gallstones that acts by inhibiting the Na⁺/H⁺ exchanger subtype 3 (NHE3), as demonstrated in LAP1 cells expressing the human NHE3 (IC₅₀ = 1.7 μM). Other compounds from this series of bile acid-substituted phenyl alkenoyl guanidines include the following:



Compound	R1	R2	R3	R4	R5	Formula
289497	Me	CH=C(Me)CO-N=C(NH2)2	H	H	OCH2Ph	C ₄₉ H ₆₄ N ₆ O ₇
289498	H	H	H	H	OCH2Ph	C ₄₃ H ₅₆ N ₃ O ₆
289499	H	H	H	H	OMe	C ₃₇ H ₅₁ N ₃ O ₆
289500	Me	CH=C(Me)CO-N=C(NH2)2	H	H	NHCH2CO2H	C ₄₄ H ₆₁ N ₇ O ₈
289501	Me	H	F	H	OH	C ₃₇ H ₅₀ FN ₃ O ₆
289502	Me	H	F	F	OH	C ₃₇ H ₄₉ F ₂ N ₃ O ₆

SOURCE – Aventis Pharma.

REFERENCES

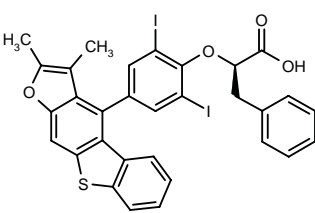
1. Weichert, A. et al. (Aventis Pharma Deutschland GmbH) *Bile-acid substd. phenyl alkenoyl guanidines, method for the production thereof, use thereof as medicaments or diagnostic agents and medicaments that contain them.* DE 19849722, WO 0024761.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

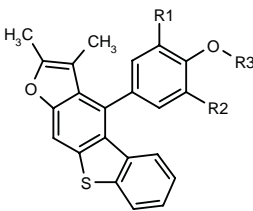
289087

2(*R*)-[4-(2,3-Dimethyl[1]benzothieno[3,2-*f*]benzofuran-4-yl)-2,6-diiodophenoxy]-3-phenylpropionic acid



C31 H22 I2 O4 S; Mol wt: 744.3768

ACTION – Protein-tyrosine-phosphatase (PTP) inhibitor found to inhibit rat hepatic microsomal PTP activity by 72.70% at 50 μM using triphosphorylated insulin receptor dodecaphosphopeptide as substrate and to give an IC₅₀ value of 0.074 μM when tested for inhibition of human recombinant PTP1B *in vitro*. In diabetic *ob/ob* mice, it lowered plasma glucose and insulin levels by 43 and 39% from controls, respectively. The compound is potentially useful for the treatment of insulin resistance associated with obesity, diabetes mellitus, glucose intolerance, hypertension and ischemic diseases of the large and small blood vessels. Other specifically claimed 4-aryl-1-oxa-9-thia-cyclopenta[*b*]fluorenes are:



Compound	R1	R2	R3	Formula
289089	H	H	Me	C ₂₃ H ₁₈ O ₂ S
289090	H	H	H	C ₂₂ H ₁₆ O ₂ S
289091	I	I	H	C ₂₂ H ₁₄ I ₂ O ₂ S
289094	I	I	(<i>R</i>)-CH(Me)CO2H	C ₂₅ H ₁₈ I ₂ O ₄ S

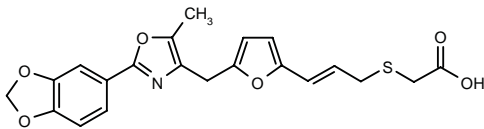
SOURCE – American Home Products.

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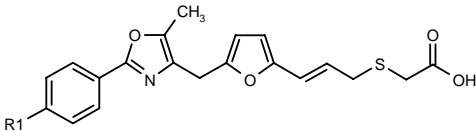
289364

2-[3-[5-[2-(1,3-Benzodioxol-5-yl)-5-methyloxazol-4-ylmethyl]furan-2-yl]-2(*E*)-propenylsulfanyl]acetic acid



C21 H19 N O6 S; Mol wt: 413.4481

ACTION – Peroxisome proliferator-activated receptor (PPAR) modulator that is reported to act preferably on PPAR α and PPAR γ subtypes, potentially useful in the treatment or prevention of diabetes, obesity, metabolic disorders, hyperlipidemia, arteriosclerosis, hypertension, circulatory diseases and ischemic heart disease. Compound was shown to significantly reduce blood sugar and triglyceride levels in KKA γ mice when given in the diet at a dose of 44 mg/kg/day x 3 days, and it also significantly reduced plasma total cholesterol, triglycerides and free fatty acids in cholesterol-fed rats given a single oral dose of 20 mg/kg. Other compounds from this series of carboxylic acid derivatives include the following:



Compound	R1	Formula
289365	H	C ₂₀ H ₁₉ NO ₄ S
289366	Me	C ₂₁ H ₂₁ NO ₄ S
289367	Et	C ₂₂ H ₂₃ NO ₄ S

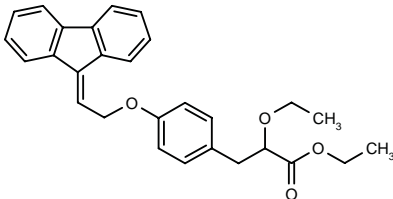
SOURCE – Ono.

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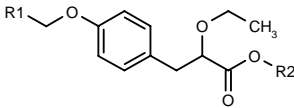
289386

2-Ethoxy-3-[4-[2-(9*H*-fluoren-9-ylidene)ethoxy]-phenyl]propionic acid ethyl ester

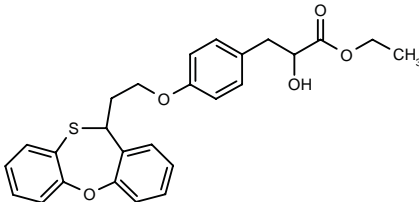


C28 H28 O4; Mol wt: 428.5252

ACTION – Peroxisome proliferator-activated receptor (PPAR) modulator that reduces blood glucose and triglyceride levels and is thus potentially useful for the treatment of diabetes and obesity. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
289387	fluoren-9-ylidene=CH	H	C ₂₆ H ₂₄ O ₄
289388	6,11-dihydro-dibenzo-[b,e]oxepin-11-ylidene=CHCH2	Et	C ₃₀ H ₃₂ O ₅
289389	6,11-dihydro-dibenzo-[b,e]oxepin-5-ylidene=CH	H	C ₂₈ H ₂₈ O ₅
289390	9-fluorenyl-CH2	Et	C ₂₈ H ₃₀ O ₄
289391	9-fluorenyl-CH2	H	C ₂₆ H ₂₆ O ₄
289393	10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene=CH	Et	C ₃₀ H ₃₂ O ₄
289394	10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene=CH	H	C ₂₈ H ₂₈ O ₄
289395	10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene=CHCH2	Et	C ₃₁ H ₃₄ O ₄
289397	10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene=CHCH2	H	C ₂₉ H ₃₀ O ₄
289398	11H-dibenzo[b,f][1,4]oxathiepin-5-yl-CH2	Et	C ₂₈ H ₃₀ O ₅ S
289401	xanthen-9-yl-CH2	Et	C ₂₈ H ₃₀ O ₅
289402	xanthen-9-yl-CH2	H	C ₂₆ H ₂₆ O ₅
289404	12H-dibenzo[d,g][1,3]dioxocin-12-ylidene=CH	Et	C ₂₈ H ₃₀ O ₆
289406	12H-dibenzo[d,g][1,3]dioxocin-12-ylidene=CH	H	C ₂₇ H ₂₆ O ₆



289400: C26 H26 O5 S

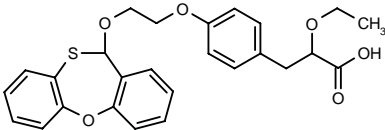
SOURCES – Novo Nordisk; Dr. Reddy's Research Foundation.

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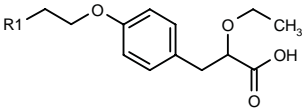
289392

3-[4-[2-(11*H*-Dibenzo[*b,f*][1,4]oxathiepin-11-yloxy)ethoxy]-phenyl]-2-ethoxypropionic acid



C26 H26 O6 S; Mol wt: 466.5514

ACTION – Peroxisome proliferator-activated receptor (PPAR) modulator that reduces blood glucose and triglyceride levels and is thus potentially useful for the treatment of diabetes and obesity. Other specifically claimed compounds include the following:



Compound	R1	Formula
289396	dibenzo[b,f][1,4]thiazepin-11-yl-NH	C ₂₆ H ₂₆ N ₂ O ₄ S
289399	10,11-dihydro-dibenzo[b,f]thiepin-10-yl-S	C ₂₇ H ₂₈ O ₄ S ₂

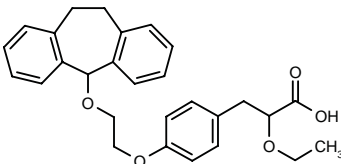
SOURCES – Novo Nordisk; Dr. Reddy’s Research Foundation.

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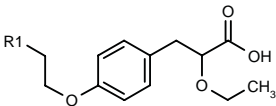
289403

3-[4-[2-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yloxy)ethoxy]phenyl]-2-ethoxypropionic acid



C28 H30 O5; Mol wt: 446.5400

ACTION – Peroxisome proliferator-activated receptor (PPAR) modulator that reduces blood glucose and triglyceride levels and is thus potentially useful for the treatment of diabetes and obesity. Other specifically claimed compounds include the following:



Compound	R1	Formula
289405	6,11-dihydro-dibenzo[b,e]oxepin-11-yl-S	C ₂₇ H ₂₈ O ₅ S
289407	10,11-dihydro-dibenzo-[a,d]cyclohepten-5-yl-N(Me)	C ₂₉ H ₃₃ NO ₄
289409	5-Me-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl-O	C ₂₈ H ₂₉ NO ₆
289412	4,9-dihydro-thieno-[2,3-c][2]benzothiepin-4-yl-O	C ₂₅ H ₂₆ O ₅ S ₂
289415	12H-dibenzo[d,g][1,3]dioxocin-12-yl-O	C ₂₇ H ₂₈ O ₇

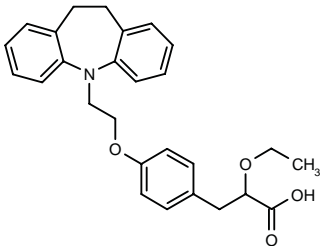
SOURCES – Novo Nordisk; Dr. Reddy’s Research Foundation.

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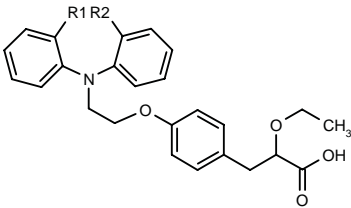
289408

3-[4-[2-(10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)ethoxy]phenyl]-2-ethoxypropionic acid



C27 H29 N O4; Mol wt: 431.5291

ACTION – Peroxisome proliferator-activated receptor (PPAR) modulator that reduces blood glucose and triglyceride levels and is thus potentially useful for the treatment of diabetes and obesity. Other specifically claimed compounds include the following:



Compound	R1,R2	Formula
289410	-CH2O-	C ₂₆ H ₂₇ NO ₅
289411	-(CH2)3-	C ₂₈ H ₃₁ NO ₄
289413	-CH2CO-	C ₂₇ H ₂₇ NO ₅
289414	-CH=C(OMe)-	C ₂₈ H ₂₉ NO ₅
289416	-SO2N(Me)-	C ₂₆ H ₂₈ N ₂ O ₆ S
289417	-CO-	C ₂₆ H ₂₅ NO ₅
289419	-SO-	C ₂₅ H ₂₅ NO ₅ S

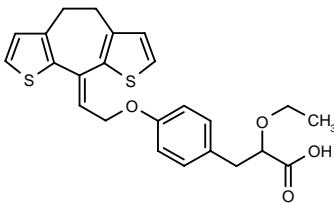
SOURCES – Novo Nordisk; Dr. Reddy’s Research Foundation.

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1. Jeppesen, L. et al. (Novo Nordisk A/S;Dr. Reddy’s Research Foundation) *New cpds., their preparation and use.* WO 0023425.

289418

3-[4-[2-(5,9-Dihydro-4*H*-cyclohepta[2,1-*b*:4,5-*b'*]-dithiophen-9-ylidene)ethoxy]phenyl]-2-ethoxypropionic acid



C24 H24 O4 S2; Mol wt: 440.5816

ACTION – Peroxisome proliferator-activated receptor (PPAR) modulator that reduces blood glucose and triglyceride levels and is thus useful for the treatment of diabetes and obesity.

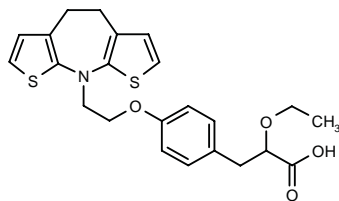
SOURCES – Novo Nordisk; Dr. Reddy’s Research Foundation.

REFERENCES

1. Jeppesen, L. et al. (Novo Nordisk A/S;Dr. Reddy’s Research Foundation) *New cpds., their preparation and use.* WO 0023445.

289420

3-[4-[2-(4,5-Dihydro-9*H*-dithieno[2,3-*b*:3’,2’-*f*]azepin-9-yl)ethoxy]phenyl]-2-ethoxypropionic acid



C23 H25 N O4 S2; Mol wt: 443.5855

ACTION – Peroxisome proliferator-activated receptor (PPAR) modulator that reduces blood glucose and triglyceride levels and is thus useful for the treatment of diabetes and obesity.

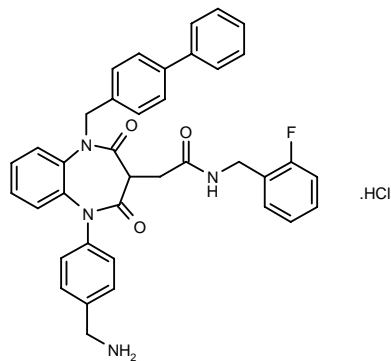
SOURCES – Novo Nordisk; Dr. Reddy’s Research Foundation.

REFERENCES

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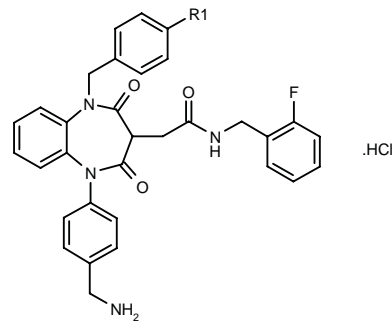
289474

2-[1-[4-(Aminomethyl)phenyl]-5-(biphenyl-4-ylmethyl)-2,4-dioxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*-(2-fluorobenzyl)acetamide hydrochloride



C38 H33 F N4 O3 . HCl; Mol wt: 649.1626

ACTION – Somatostatin receptor modulator with potential in the treatment of diabetes, obesity, diabetic complications or intractable diarrhea. A representative compound from a series of 1,5-benzodiazepine derivatives, wherein the following are also included:



Compound	R1	Formula
289475	4-MeO-PhCONH	C ₄₀ H ₃₇ ClFN ₅ O ₅
289476	2-Cl-PhCONH	C ₃₉ H ₃₄ Cl ₂ FN ₅ O ₄
289477	3-thienyl	C ₃₆ H ₃₂ ClFN ₄ O ₃ S
289478	CF3	C ₃₃ H ₂₉ ClF ₄ N ₄ O ₃

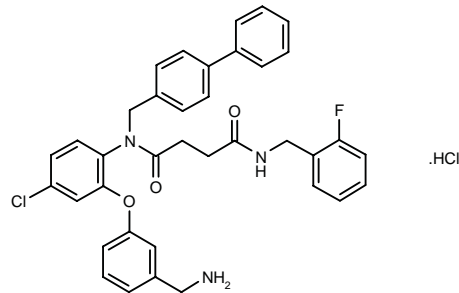
SOURCE – Takeda.

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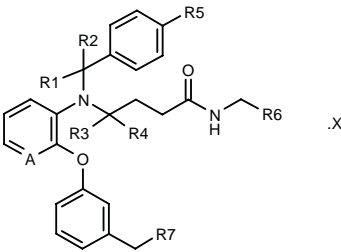
289480

*N*¹-[2-[3-(Aminomethyl)phenoxy]-4-chlorophenyl]-*N*¹-(biphenyl-4-ylmethyl)-*N*⁴-(2-fluorobenzyl)succinamide hydrochloride



C37 H33 Cl F N3 O3 . HCl; Mol wt: 658.5976

ACTION – Somatostatin receptor modulator expected to be useful for the treatment of diabetes, acromegaly, diabetic neuropathy, obesity, eating disorders, pancreatitis, peptic ulcers and *Helicobacter pylori*-related disorders, diarrhea, irritable bowel syndrome and cancer, among other indications. A representative compound from a series of aromatic amine derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	R6	R7	A	X	Formula
289483		-O-	H	H	Ph	2-F-Ph	CH2-NH2	N	HCl	C ₃₇ H ₃₅ FN ₄ O ₃ .ClH
289484	H	H	-O-	H	2-CF3-Ph		NH2	CH	CF3CO2H	C ₃₂ H ₃₀ F ₃ N ₃ O ₃ .C ₂ HF ₃ O ₂
289485	H	H	-O-	OPh	2,6-(F)2-Ph		NH2	CH	CF3CO2H	C ₃₇ H ₃₃ F ₂ N ₄ O ₄ .C ₂ HF ₃ O ₂
289487	H	H	-O-	OPh	1-pyrrolidinyl-CH2		NH2	CH	CF3CO2H	C ₃₆ H ₄₀ N ₄ O ₄ .C ₂ HF ₃ O ₂

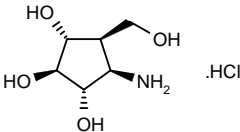
SOURCE – Takeda.

REFERENCES

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289527

(1*R*,2*S*,3*S*,4*R*,5*R*)-4-Amino-5-(hydroxymethyl)cyclopentane-1,2,3-triol hydrochloride



C₆ H₁₃ N O₄ . HCl; Mol wt: 199.6326

ACTION – Potent and selective inhibitor of β-glucosidase (K_i = 0.18 and 3.4 μM, respectively, against enzyme extracted from *Caldocellum saccharolyticum* and almonds), at least 100-fold less potent against α-glucosidase, β-galactosidase and α-mannosidase (K_i = 13, 41 and 180 μM, respectively). Potentially useful for the treatment of diabetes, cancer, viral and bacterial infections, as well as an insecticide.

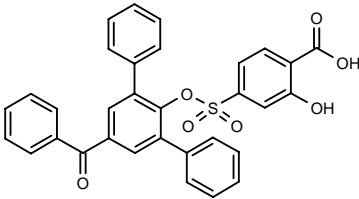
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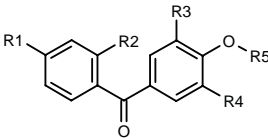
289664

4-(5'-Benzoyl[1,1':3',1'']terphenyl-2'-yloxysulfonyl)-2-hydroxybenzoic acid



C₃₂ H₂₂ O₇ S; Mol wt: 550.5848

ACTION – Agent for the treatment of metabolic disorders related to insulin resistance or hyperglycemia, a protein-tyrosine-phosphatase (PTPase) inhibitor (IC₅₀ = 0.354 μM against human recombinant PTP1B). Other specifically claimed compounds from this series of benzophenone derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
289665	H	H	Ph	Ph	CH2CO2H	C ₂₇ H ₂₀ O ₄
289666	H	H	Ph	Ph	4-CO2H-3-OH-PhCH2	C ₃₃ H ₂₄ O ₅
289667	H	H	I	I	4-AcO-3-(CO2Me)-PhCH2	C ₂₄ H ₁₈ O ₆
289668	H	H	Ph	Ph	4-(CO2Et)-3-OH-PhSO2	C ₃₄ H ₂₆ O ₇ S
289669	OMe	H	H	H	4-CO2H-3-OH-PhSO2	C ₂₁ H ₁₆ O ₈ S
289670	OMe	H	I	I	4-CO2H-3-OH-PhSO2	C ₂₁ H ₁₄ O ₈ S
289671	OMe	H	Ph	Ph	4-CO2H-3-OH-PhSO2	C ₃₃ H ₂₄ O ₈ S
289672	H	H	3-thienyl	3-thienyl	4-CO2H-3-OH-PhSO2	C ₂₈ H ₁₈ O ₇ S ₃
289673	H	H	Ph	Ph	4-CO2H-PhSO2	C ₃₂ H ₂₂ O ₆ S
289674	H	Cl	Ph	H	4-CO2H-3-OH-PhSO2	C ₂₈ H ₁₇ ClO ₇ S
289675	H	H	I	I	4-CO2H-3-OH-PhSO2	C ₂₀ H ₁₂ O ₇ S

SOURCE – American Home Products.

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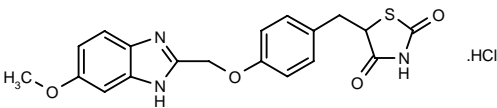
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CI-1037

281436

(±)-5-[4-(6-Methoxy-1*H*-benzimidazol-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione hydrochloride

CS-011



C₁₉ H₁₇ N₃ O₄ S . HCl; Mol wt: 419.8872

ACTION – Antidiabetic agent, a thiazolidinedione with superior potency compared to rosiglitazone in rodent models of type 2 diabetes including 9-week-old ZDF (Zucker diabetic fatty) rats, *db/db* mice and KK mice. In these models, compound exhibited 8-141-fold greater potency than rosiglitazone in lowering blood glucose levels. In addition, at doses of 0.01 mg/kg/day for 7 weeks it normalized glucose tolerance and hypertriglyceridemia and reduced free fatty acids in ZDF rats. *In vitro* studies demonstrated its ability to activate PPAR γ receptors (IC_{50} = 160 nM) and to induce the differentiation of 3T3 L1 cells into adipocytes (EC_{50} = 5 nM).

SOURCES – Pfizer; Sankyo.

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3. Pulaski, J.T. et al. *The antidiabetic effects of CI-1037/CS011, a new thiazolidinedione*. Diabetes 2000, 49(Suppl. 1): Abst 496-P.
4. Sankyo to turn joint venture into subsidiary to market products in U.S.. DailyDrugNews.com (Daily Essentials) 1999, Dec 21.
5. Six new drug candidates enter the R&D pipeline at Sankyo. DailyDrugNews.com (Daily Essentials) 1999, Oct 15.

HMR-1964

290052

3B-L-Lysine-29B-glutamic acid insulin (human)

[Lys(B3),Glu(B29)]-insulin (human)

ACTION – Insulin analogue that preferentially activates insulin receptor IRS-2 signaling in K6 myoblasts, while being only marginally active at the IRS-1 receptor. Considered an attractive candidate for further development as a potential antidiabetic agent. Another novel insulin analogue is:

3B-L-Lysine-28B-L-isoleucineinsulin (human)

HMR-1153 [290053]

SOURCE – Aventis Pharma.

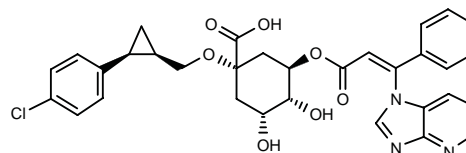
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S-4048*

229186

(1*S*,3*R*,4*R*,5*R*)-1-[(1*R*,2*S*)-2-(4-Chlorophenyl)cyclopropylmethoxy]-3,4-dihydroxy-5-[3-(1*H*-imidazo[4,5-*b*]pyridin-1-yl)-3-phenyl-2(*Z*)-propenoyloxy]cyclohexane-1-carboxylic acid



C32 H30 Cl N3 O7; Mol wt: 604.0650

ACTION – Antidiabetic agent, an inhibitor of glucose-6-phosphatase (G-6-Pase; IC_{50} = 9.4 nM) proven to block G-6-P translocation into intact and permeabilized rat liver microsomes. The inhibition of G-6-P transport by compound was associated with inhibition of the rate of glucose output from rat hepatocytes in the presence of a maximally stimulatory concentration of glucagon (IC_{50} = 320 nM). Compound also inhibited the basal rate of glucose production by rat hepatocytes by 47%. *In vivo*, compound given i.p. to fasted mice or rats was seen to lower dose-dependently the circulating plasma glucose concentration, with a maximal effect of 71 and 36%, respectively, at 30 min after 100 mg/kg. This effect declined until it was fully reversed by 3 h postdosing. Studies on hepatic and plasma lipid metabolism in rats demonstrated that the acute inhibition of G-6-Pase leads to acute stimulation of fat synthesis and development of fatty liver, without affecting hepatic VLDL secretion.

SOURCE – Aventis Pharma.

REFERENCES

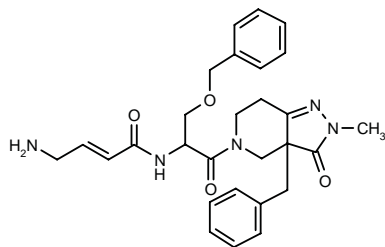
1. Hemmerle, H. et al. (Aventis SA) *Cyclohexane derivs., processes for their preparation and their use as glucose-6-phosphatase inhibitors*. CA 2149007, CA 4416433, EP 0682024, JP 1995330767, US 5739147.
2. Burger, H.-J. et al. *Pharmacological interference with hepatic glucose production*. Ann New York Acad Sci 1999, 892: 312.
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5. Weigman, C.H. et al. *Acute inhibition of glucose-6-phosphatase by S4048 leads to increased de novo lipogenesis and development of fatty liver without affecting VLDL production in rats*. Diabetes 2000, 49(Suppl. 1): Abst 1214-P.

*Identified compound **229186** Drug Data Rep 1996, 018(03): 0249.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

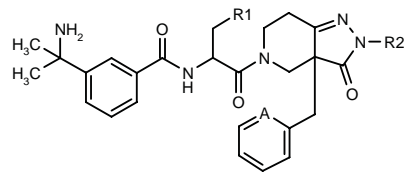
288862

4-Amino-*N*-[2-(3a-benzyl-2-methyl-3-oxo-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*]pyridin-5-yl)-2-oxo-1-(benzyloxymethyl)ethyl]-2(*E*)-butenamide

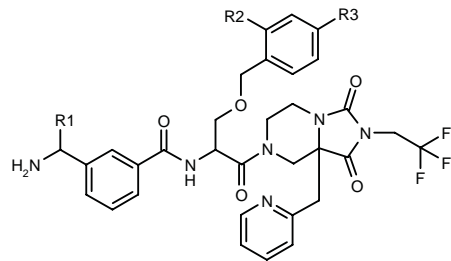


C28 H33 N5 O4; Mol wt: 503.5997

ACTION – Growth hormone (GH) secretagogue potentially useful for treating growth hormone deficiencies, osteoporosis, congestive heart failure, obesity, frailty associated with aging, AIDS- or cancer-associated cachexia and for accelerating bone fracture repair, wound healing and the recovery of burn patients or patients after major surgery. Other compounds from this series of dipeptide derivatives include the following:



Compound	R1	R2	A	Formula
288865	OCH2Ph	H	CH	C ₃₃ H ₃₇ N ₅ O ₄
288866	3-indolyl	Me	CH	C ₃₅ H ₃₈ N ₆ O ₃
288868	2,4-(F)2-PhCH2O	CH2CF3	N	C ₃₄ H ₃₅ F ₅ N ₆ O ₄



Compound	R1	R2	R3	Formula
288871	Me	F	F	C ₃₃ H ₃₃ F ₅ N ₆ O ₅
288872	H	H	H	C ₃₂ H ₃₃ F ₃ N ₆ O ₅

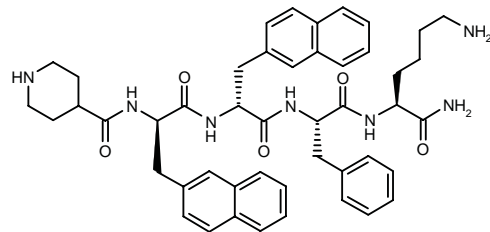
SOURCE – Pfizer.

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289634

N-(4-Piperidinylcarbonyl)-*D*-(2-naphthyl)alanyl-*D*-(2-naphthyl)alanyl-*L*-phenylalanyl-*L*-lysινamide



C47 H55 N7 O5; Mol wt: 797.9955

ACTION – A representative compound from a series of low-molecular-weight peptidomimetic growth hormone (GH) secretagogues useful for promoting growth, either alone or in combination with a growth factor such as IGF-1, as well as for the treatment of type 2 diabetes. *In vitro*, compound was shown to increase the release of GH in a rat anterior pituitary cell assay with an EC₅₀ value of 0.18 ± 0.04 nM, while having no effect on TSH, FSH, LH and ACTH. *In vivo*, it exhibited anabolic effects in rats when administered using osmotic minipump, inducing significant body weight and organ weight gains; these effects were potentiated when given in combination with IGF-1.

SOURCE – Genentech.

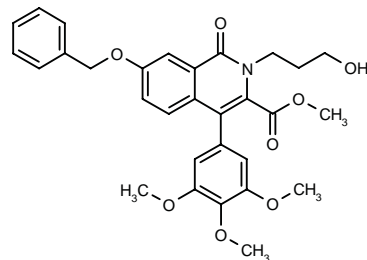
REFERENCES

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TREATMENT OF MALE SEXUAL DYSFUNCTION

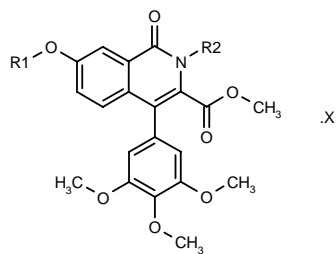
288745

7-Benzyloxy-2-(3-hydroxypropyl)-1-oxo-4-(3,4,5-trimethoxyphenyl)-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester

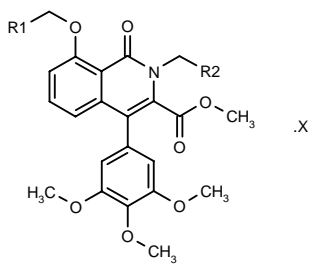


C30 H31 N O8; Mol wt: 533.5739

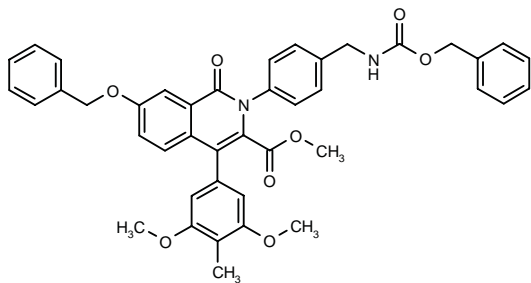
ACTION – A representative compound from a series of isoquinoline derivatives with phosphodiesterase type 5 (PDE5)-inhibitory activity, reported to be effective for the treatment of male erectile dysfunction and cardiovascular disorders, wherein the following are also included:



Compound	R1	R2	X	Formula
288751	H	3-Pyr-CH2		C ₂₆ H ₂₄ N ₂ O ₇
288752	H	4-(t-BuOCONHCH2)-Ph		C ₃₂ H ₃₄ N ₂ O ₉
288754	2-Pyr-CH2	3-Pyr-CH2	2HCl	C ₃₂ H ₂₉ N ₃ O ₇ ·2HCl
288756	6-(CH2OH)-2-Pyr-CH2	N(Me)2	HCl	C ₂₈ H ₂₉ N ₃ O ₇ ·HCl
288759	H	CH2CH2CONH2		C ₂₃ H ₂₄ N ₂ O ₈
288761	2-Pyr-CH2	2-Me-4-Pyr-CH2	2HCl	C ₃₃ H ₃₁ N ₃ O ₇ ·2HCl



Compound	R1	R2	X	Formula
288758	Ph	H		C ₂₈ H ₂₇ NO ₇
288763	2-Pyr	2-Me-4-Pyr	2HCl	C ₃₃ H ₃₁ N ₃ O ₇ ·2HCl



288747: C42 H38 N2 O8

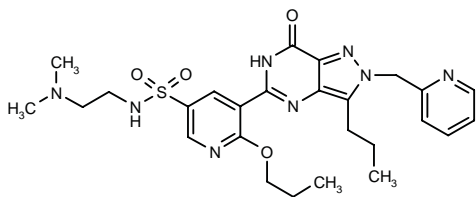
SOURCE – Tanabe Seiyaku.

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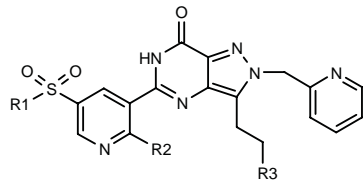
288811

N-[2-(Dimethylamino)ethyl]-5-[7-oxo-3-propyl-2-(2-pyridinylmethyl)-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-6-propoxypyridine-3-sulfonamide



C26 H34 N8 O4 S; Mol wt: 554.6726

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 8.50 nM) for the treatment of male erectile and female sexual dysfunction. Other exemplified pyrazolo-pyrimidone derivatives are:



Compound	R1	R2	R3	Formula
288812	4-Et-1-Pip	OEt	H	C ₂₇ H ₃₃ N ₇ O ₄ S
288813	3-OH-1-azetidinyI	OPr	Me	C ₂₅ H ₂₉ N ₇ O ₅ S
288815	1-(EtOCO)-4-Pip-NH	OPr	Me	C ₃₀ H ₃₈ N ₆ O ₆ S
288816	N(Me)2	OEt	Me	C ₂₃ H ₂₇ N ₇ O ₄ S
288817	4-Et-1-Pip	CH2OEt	H	C ₂₈ H ₃₅ N ₇ O ₄ S

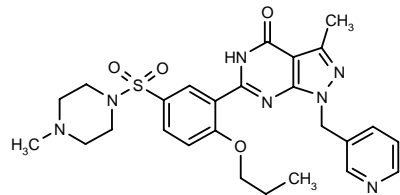
SOURCE – Pfizer.

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1. Wood, A. (Pfizer Inc.;Pfizer Ltd.) Pyrazolopyrimidinone cGMP PDE5 inhibitors for the treatment of sexual dysfunction. EP 0995750, JP 2000128883, WO 0024745.

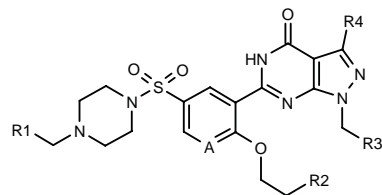
288818

3-Methyl-6-[5-(4-methylpiperazin-1-ylsulfonyl)-2-propoxyphenyl]-1-(3-pyridinylmethyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one



C26 H31 N7 O4 S; Mol wt: 537.6419

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 4.40 nM) for the treatment of male erectile and female sexual dysfunction. Other exemplified pyrazolo-pyrimidone derivatives are:



Compound	R1	R2	R3	R4	A	Formula
288819	Me	Me	Et	3-Pyr-CH2	CH	C ₂₉ H ₃₇ N ₇ O ₄ S
288820	H	H	Et	CH2Ph	CH	C ₂₈ H ₃₄ N ₆ O ₄ S
288821	Me	H	Me	2-pyrazinyl	N	C ₂₄ H ₂₉ N ₉ O ₄ S
288822	Me	H	Et	2-pyrazinyl	N	C ₂₅ H ₃₁ N ₉ O ₄ S
288823	Me	H	Me	Ph	N	C ₂₆ H ₃₁ N ₇ O ₄ S

SOURCE – Pfizer.

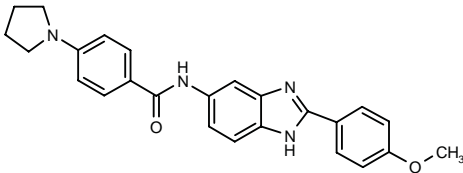
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CONTRACEPTIVES

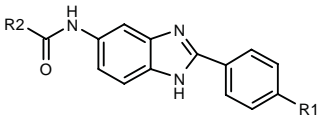
289697

N-[2-(4-Methoxyphenyl)-1*H*-benzimidazol-5-yl]-4-(1-pyrrolidinyl)benzamide



C25 H24 N4 O2; Mol wt: 412.4906

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist shown to inhibit [¹²⁵I]-leuporelin binding in CHO cells expressing the human GnRH receptor with an IC₅₀ value of 0.04 μM. It is considered to have potential utility in the prevention and treatment of sex hormone-dependent diseases, for birth control and for modulating the menstrual cycle. Other exemplified compounds from this series of benzimidazole derivatives include the following:



Compound	R1	R2	Formula
289698	OMe	4-(EtNHCONH)-Ph	C ₂₄ H ₂₃ N ₅ O ₃
289699	OMe	3-NO ₂ -Ph	C ₂₁ H ₁₆ N ₄ O ₄
289700	OMe	4-(CO ₂ Me)-Ph	C ₂₃ H ₁₉ N ₃ O ₄
289701	t-Bu	4-NO ₂ -Ph	C ₂₄ H ₂₂ N ₄ O ₃
289702	i-PrO	4-NO ₂ -Ph	C ₂₃ H ₂₀ N ₄ O ₄

SOURCE – Takeda.

REFERENCES

1. Suzuki, N. et al. (Takeda Chemical Industries, Ltd.) *Gonadotropin releasing hormone antagonists*. JP 2000095767.

LUNELLE™

282496

Combination of medroxyprogesterone acetate and estradiol cypionate

Cyclo-Provera (formerly)
Lune™
Lunella™

ACTION – Once-monthly injectable contraceptive that contains estrogen and progestin and may offer women a reliable and convenient form of birth control. Compound is currently awaiting approval by the FDA and it is also under review in Europe.

SOURCE – Pharmacia.

REFERENCES

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2. Jain, J.K. et al. *Comparison of ovarian follicular activity during treatment with a monthly injectable contraceptive and a low-dose oral contraceptive*. Contraception 2000, 61(3): 195.

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4. Kaunitz, A.M., Mischell, D.R. Jr. *Lunelle monthly contraceptive injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension): A contraceptive method for women in the US and world-wide*. Contraception 1999, 60(4): 177.

5. Kaunitz, A.M. *Long-acting hormonal contraception: Assessing impact on bone density, weight and mood*. Int J Fertil Women Med 1999, 44(2): 110.

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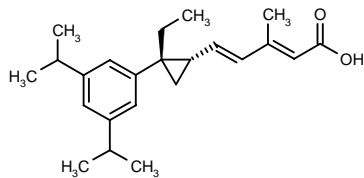
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DERMATOLOGIC DRUGS

ACNE THERAPY

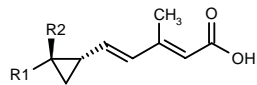
288744

(+)-5-[(1*S*,2*S*)-2-(3,5-Diisopropylphenyl)-2-ethylcyclopropyl]-3-methyl-2(*E*),4(*E*)-pentadienoic acid



C23 H32 O2; Mol wt: 340.5038

ACTION – Selective retinoid X receptor (RXR) agonist with potential in the treatment of skin diseases such as actinic keratoses, acne, psoriasis and atopic dermatitis, as well as for the treatment of metabolic diseases, hyperproliferative diseases including cancer and certain ophthalmological diseases. Compound exhibited EC₅₀ values of 0.0003, 0.06 and 0.0006 nM, respectively, for RXRα, RXRβ and RXRγ receptors in a transactivation assay, and K_d values of 0.05 and 7.3 nM, respectively, for RXRα and RXRγ receptors in a binding assay. Other compounds from this series of 2,4-pentadienoic acid derivatives include the following:



Compound	R1	R2	Isomer	Formula
288746	3,5-(<i>t</i> -Bu)2-Ph	Pr	(+)-(1 <i>S</i> ,2 <i>S</i>)	C ₂₆ H ₃₈ O ₂
288748	8- <i>t</i> -Bu-5,5-(Me)2-5,6-dihydro-2-Naph	Pr	(+)-(1 <i>S</i> ,2 <i>S</i>)	C ₂₈ H ₃₈ O ₂
288749	2,2,4-(Me)3-2H-1-benzopyran-7-yl	Me	(1 <i>S</i> ,2 <i>S</i>)	C ₂₂ H ₂₆ O ₃
288750	8- <i>i</i> -Pr-5,5-(Me)2-5,6-dihydro-2-Naph	Pr	(+)-(1 <i>S</i> ,2 <i>S</i>)	C ₂₇ H ₃₆ O ₂

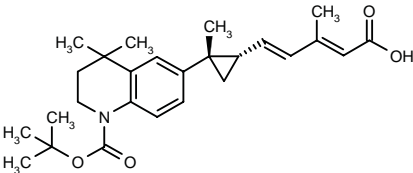
SOURCE – Allergan.

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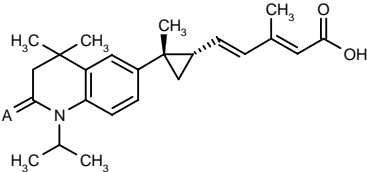
288753

5-[(1*S*,2*S*)-2-[1-(*tert*-Butoxycarbonyl)-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl]-2-methylcyclopropyl]-3-methyl-2(*E*),4(*E*)-pentadienoic acid



C26 H35 N O4; Mol wt: 425.5655

ACTION – Selective retinoid X receptor (RXR) agonist with potential in the treatment of skin diseases such as actinic keratoses, acne, psoriasis and atopic dermatitis, as well as for the treatment of metabolic diseases, hyperproliferative diseases including cancer and certain ophthalmological diseases. Compound exhibited EC₅₀ values of 0.00015, 0.00042 and 0.00031 nM, respectively, for RXRα, RXRβ and RXRγ receptors in a transactivation assay, and K_d values of 0.35 and 4.1 nM, respectively, for RXRα and RXRγ receptors in a binding assay; selectivity over retinoic acid receptors (RAR) was demonstrated in binding assays by K_d values of 12,000, > 30,000 and 10,000 nM, respectively, for RARα, RARβ and RARγ receptors. Other compounds from this series of tetrahydroquinoline derivatives include the following:



Compound	A	Formula
288755	O	C ₂₄ H ₃₁ NO ₃
288757	S	C ₂₄ H ₃₁ NO ₂ S

SOURCE – Allergan.

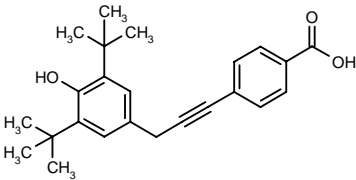
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ANTIPSORIATICS

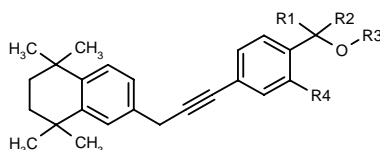
287717

4-[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1-propynyl]-benzoic acid



C24 H28 O3; Mol wt: 364.4822

ACTION – Agent with cell differentiation- and cell proliferation-modulating activity and potential in the topical or systemic treatment of dermatological conditions related to keratinization disorders or having an inflammatory and/or immunoallergic component, benign or malignant dermal or epidermal proliferative disorders, connective tissue degenerative disorders, cicatrization disorders and corneopathies, for combatting skin aging, as well as for the treatment of inflammatory disorders, cancerous and precancerous conditions, alopecia, cardiovascular disorders and insulin-dependent diabetes. Other compounds from this series of propynyl or dienyl biaromatic derivatives include the following:



Compound	R1	R2	R3	R4	Formula
287719		-O-	H	H	C ₂₄ H ₂₆ O ₂
287720		-O-	Me	OH	C ₂₅ H ₂₈ O ₃
287721	H	H	H	OH	C ₂₄ H ₂₈ O ₂

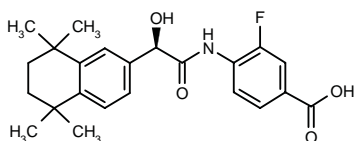
SOURCE – Galderma.

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287749

3-Fluoro-4-[2(*R*)-hydroxy-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)acetamido]benzoic acid



C23 H26 F N O₄; Mol wt: 399.4594

ACTION – Enantiomer of a previously reported selective retinoic acid receptor γ (RAR γ) agonist that has been shown to be responsible for all of the retinoid activity of the parent racemic compound. In transactivation assays in transfected HeLa cells, compound exhibited an EC₅₀ value of 20 nM for RAR γ , while it was not active at RAR α and the EC₅₀ for RAR β was 300 nM. *In vivo*, it significantly prevented the conversion of papillomas to malignant tumors in a murine skin carcinogenesis assay using DMBA and TPA as initiator and promoter, respectively, when given at 15 and 30 mg/kg i.p., while 13-*cis*-retinoic acid at 50 mg/kg i.p. was inactive. Claimed for the treatment of dermatological disorders such as acne, psoriasis, premalignant lesions and actinic keratoses, as well as for the prevention of spontaneous squamous cell carcinoma in immunocompromised human transplant patients.

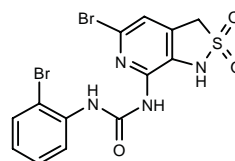
SOURCE – Bristol-Myers Squibb.

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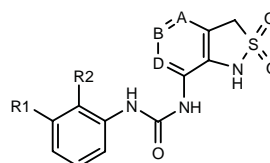
288942

N-(5-Bromo-2,2-dioxo-1,3-dihydroisothiazolo[3,4-*c*]pyridin-7-yl)-*N'*-(2-bromophenyl)urea



C13 H10 Br₂ N₄ O₃ S; Mol wt: 462.1210

ACTION – CXCR1/CXCR2 (IL-8 α /IL-8 β) receptor antagonist with potential in the treatment of chemokine-mediated disorders such as psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, septic shock, stroke, reperfusion injury, glomerulonephritis, thrombosis, restenosis, angiogenesis, malaria, bone resorption disorders, Alzheimer's disease and transplant rejection. A representative compound from a series of cyclic pyridyl derivatives, wherein the following are also included:



Compound	R1	R2	A	B	D	Formula
288943	H	Br	CH	C(Cl)	N	C ₁₃ H ₁₀ BrClN ₄ O ₃ S
288944	Cl	Cl	CH	C(CN)	N	C ₁₄ H ₉ Cl ₂ N ₅ O ₃ S
288945	H	Br	N	CH	CH	C ₁₃ H ₁₁ BrN ₄ O ₃ S
288946	H	Br	CH	N	CH	C ₁₃ H ₁₁ BrN ₄ O ₃ S
288947	H	H	CH	N	CH	C ₁₃ H ₁₂ N ₄ O ₃ S
288948	Cl	Cl	C(CN)	N	CH	C ₁₄ H ₉ Cl ₂ N ₅ O ₃ S

SOURCE – SmithKline Beecham.

REFERENCES

1. Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists.* WO 0021963.

WOUND-HEALING AGENTS

FGFR5

289728

Fibroblast growth factor receptor 5

ACTION – Human protein that belongs to the fibroblast growth factor (FGF) receptor family of proteins, which play important roles in tissue repair and regeneration. Nucleic acid molecules encoding this protein, expression vectors, host cells, recombinant methods for its production, screening methods for identifying agonists and antagonists thereof, as well as methods for the diagnosis of disease states related to its aberrant expression and for the treatment of defects in wound healing, mucositis, defects in angiogenesis, ischemia, host defense dysfunction, endocrine dysfunction, disorders of immune function and disorders of insulin secretion, are also described.

SOURCE – Human Genome Sciences.

REFERENCES

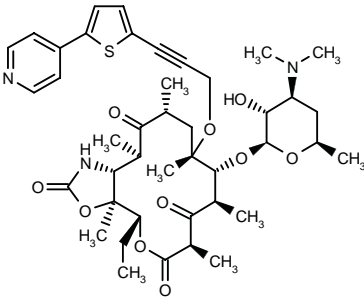
1. Ruben, S.M. and Young, P.E. (Human Genome Sciences, Inc.) *Fibroblast growth factor receptor-5*. WO 0024756.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

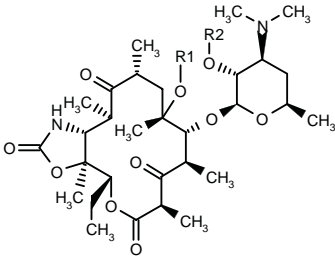
288828

11-Amino-3-des(hexopyranosyloxy)-11-desoxy-3-oxo-6-O-[3-[5-(4-pyridinyl)thien-2-yl]-2-propynyl]erythromycin A 11-N,12-O-cyclic carbamate



C42 H57 N3 O10 S; Mol wt: 795.9893

ACTION – Macrolide antibiotic proven to be more active than erythromycin A against several microorganisms, for example *Staphylococcus aureus* ATCC 6538P, *S. aureus* A5177, *S. aureus* CMX 642A, *Streptococcus pyogenes* 930, *S. pyogenes* PIU 2548 and *Streptococcus pneumoniae* 5979. A representative compound from a series of 6-O-substituted ketolides, wherein the following are also included:



Compound	R1	R2	Formula
288829	5-(5-CN-3-Pyr)-2-thienyl-ethylene-CH2	H	C ₄₃ H ₅₆ N ₄ O ₁₀ S
288832	2-(2-pyrazinyl)-5-thiazolyl-CH=CH	Ac	C ₄₁ H ₅₇ N ₅ O ₁₁ S
288833	5-(2-pyrazinyl)-2-thienyl-CH=CH	H	C ₄₀ H ₅₆ N ₄ O ₁₀ S

SOURCE – Abbott.

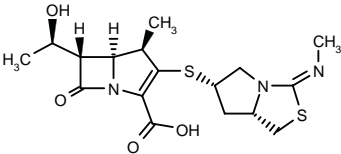
REFERENCES

1. Or, Y.S. et al. (Abbott Laboratories Inc.) *6-O-Substd. macrolides having antibacterial activity*. US 6054435.

289175

(4*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-4-methyl-3-[(6*S*,7*aS*)-3-(methylimino)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazol-6-ylsulfanyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-3-[(6*S*,7*aS*)-3-(methylimino)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazol-6-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid



C17 H23 N3 O4 S2; Mol wt: 397.5177

ACTION – Carbapenem antibiotic with potent *in vitro* activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* Terajima, *Streptococcus pyogenes* Cook, *Bacillus subtilis* ATCC6633, *Micrococcus luteus* ATCC9341, *Escherichia coli* NIHJ JC-2, *Klebsiella pneumoniae* PCI-602, *Salmonella typhi* 901, *Proteus vulgaris* OX-19 and *Pseudomonas aeruginosa* NCTC10490 (MIC = 0.013, 0.025, 0.2, 0.1, 0.1, 0.2, 0.1, 0.39 and 12.5 µg/ml, respectively), as well as low toxicity.

SOURCE – Wyeth-Lederle Japan.

REFERENCES

1. Tamai, K. et al. (Wyeth-Lederle Japan, Ltd.) *Carbapenem cpds*. JP 2000086667.

WOUND-HEALING AGENTS

FGFR5

289728

Fibroblast growth factor receptor 5

ACTION – Human protein that belongs to the fibroblast growth factor (FGF) receptor family of proteins, which play important roles in tissue repair and regeneration. Nucleic acid molecules encoding this protein, expression vectors, host cells, recombinant methods for its production, screening methods for identifying agonists and antagonists thereof, as well as methods for the diagnosis of disease states related to its aberrant expression and for the treatment of defects in wound healing, mucositis, defects in angiogenesis, ischemia, host defense dysfunction, endocrine dysfunction, disorders of immune function and disorders of insulin secretion, are also described.

SOURCE – Human Genome Sciences.

REFERENCES

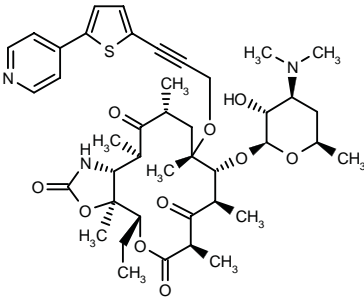
1. Ruben, S.M. and Young, P.E. (Human Genome Sciences, Inc.) *Fibroblast growth factor receptor-5*. WO 0024756.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

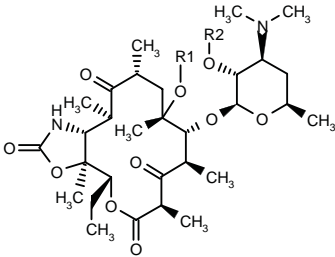
288828

11-Amino-3-des(hexopyranosyloxy)-11-desoxy-3-oxo-6-O-[3-[5-(4-pyridinyl)thien-2-yl]-2-propynyl]erythromycin A 11-N,12-O-cyclic carbamate



C42 H57 N3 O10 S; Mol wt: 795.9893

ACTION – Macrolide antibiotic proven to be more active than erythromycin A against several microorganisms, for example *Staphylococcus aureus* ATCC 6538P, *S. aureus* A5177, *S. aureus* CMX 642A, *Streptococcus pyogenes* 930, *S. pyogenes* PIU 2548 and *Streptococcus pneumoniae* 5979. A representative compound from a series of 6-O-substituted ketolides, wherein the following are also included:



Compound	R1	R2	Formula
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288832	2-(2-pyrazinyl)-5-thiazolyl-CH=CH	Ac	C ₄₁ H ₅₇ N ₅ O ₁₁ S
288833	5-(2-pyrazinyl)-2-thienyl-CH=CH	H	C ₄₀ H ₅₆ N ₄ O ₁₀ S

SOURCE – Abbott.

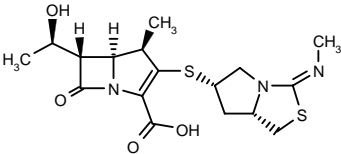
REFERENCES

1. Or, Y.S. et al. (Abbott Laboratories Inc.) *6-O-Substd. macrolides having antibacterial activity*. US 6054435.

289175

(4*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-4-methyl-3-[(6*S*,7*aS*)-3-(methylimino)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazol-6-ylsulfanyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-3-[(6*S*,7*aS*)-3-(methylimino)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazol-6-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid



C17 H23 N3 O4 S2; Mol wt: 397.5177

ACTION – Carbapenem antibiotic with potent *in vitro* activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* Terajima, *Streptococcus pyogenes* Cook, *Bacillus subtilis* ATCC6633, *Micrococcus luteus* ATCC9341, *Escherichia coli* NIHJ JC-2, *Klebsiella pneumoniae* PCI-602, *Salmonella typhi* 901, *Proteus vulgaris* OX-19 and *Pseudomonas aeruginosa* NCTC10490 (MIC = 0.013, 0.025, 0.2, 0.1, 0.1, 0.2, 0.1, 0.39 and 12.5 µg/ml, respectively), as well as low toxicity.

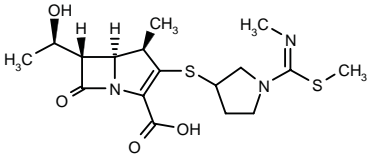
SOURCE – Wyeth-Lederle Japan.

REFERENCES

1. Tamai, K. et al. (Wyeth-Lederle Japan, Ltd.) *Carbapenem cpds*. JP 2000086667.

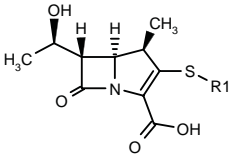
289214

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[1-[(methyl-imino)(methylsulfanyl)methyl]pyrrolidin-3-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid isomer A



C17 H25 N3 O4 S2; Mol wt: 399.5335

ACTION – Carbapenem antibiotic with potent *in vitro* activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* Terajima, *Streptococcus pyogenes* Cook, *Bacillus subtilis* ATCC6633, *Micrococcus luteus* ATCC9341, *Escherichia coli* NIHJ JC-2, *Klebsiella pneumoniae* PCI-602, *Salmonella typhi* 901, *Proteus vulgaris* OX-19 and *Pseudomonas aeruginosa* NCTC10490 (MIC = 0.025, 0.05, 0.2, 0.2, 0.2, 0.1, 0.2, 0.39 and 12.5 µg/ml, respectively) and low toxicity. Other exemplified compounds include the following:



Compound	R1	Formula
289215	1-[MeN=C(SMe)]-3-pyrrolidinyl	C ₁₇ H ₂₅ N ₃ O ₄ S ₂
289216	CH2CH2NHC(SMe)=NMe	C ₁₅ H ₂₃ N ₃ O ₄ S ₂
289217	1-[MeN=C(SMe)]-3-azetidiny	C ₁₆ H ₂₃ N ₃ O ₄ S ₂

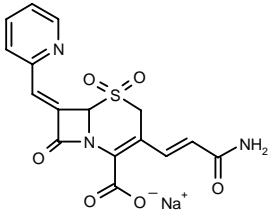
SOURCE – Wyeth-Lederle Japan.

REFERENCES

1. Tamai, K. et al. (Wyeth-Lederle Japan, Ltd.) *Carbapenem cpds.* JP 2000086660.

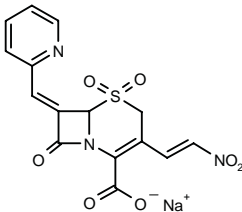
290167

3-[3-Amino-3-oxo-1(*E*)-propenyl]-1,1-dioxo-7-[(*Z*)-2-pyridylmethylene]-3-cephem-4-carboxylic acid sodium salt



C16 H12 N3 Na O6 S; Mol wt: 397.3418

ACTION – Cephalosporin β-lactamase inhibitor proven to inhibit representative class A and class C serine β-lactamases including TEM-1 and PC1 (class A; IC₅₀ = 0.09 and 0.1 µM, respectively) and P99 and GC1 (class C; IC₅₀ = 0.026 and 0.01 µM, respectively). Another 3-substituted-7-(alkylidene)cephalosporin sulfone is:



290169: C15 H10 N3 Na O7 S

SOURCE – Southern Methodist University, Dallas, TX (US).

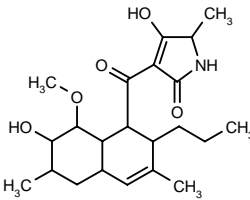
REFERENCES

1. Buynak, J.D. et al. *The synthesis and evaluation of 3-substituted-7-(alkylidene)cephalosporin sulfones as beta-lactamase inhibitors.* Bioorg Med Chem Lett 2000, 10(9): 853.

BE-54476

289177

4-Hydroxy-3-(7-hydroxy-8-methoxy-3,6-dimethyl-2-propyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-ylcarbonyl)-5-methyl-2,5-dihydro-1*H*-pyrrol-2-one



C22 H33 N O5; Mol wt: 391.5047

ACTION – Antibiotic isolated from *Streptomyces* sp. A54476 (FERM P-16839), active against *Bacillus subtilis* ATCC 6633, *Bacillus cereus* IFO 3001, methicillin-resistant *Staphylococcus aureus* MRSA 6117 and MRSA 6118, *Enterococcus faecalis* IFO 12580 and *S. aureus* FDA 209P (MIC = 3.13-6.25 µg/ml).

SOURCE – Banyu.

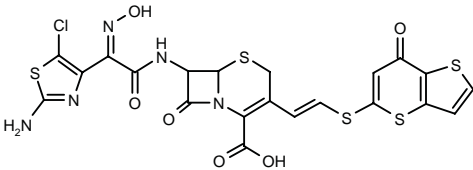
REFERENCES

1. Tsukamoto, M. et al. (Banyu Pharmaceutical Co., Ltd.) *Antibacterial substance BE-54476 and its preparation method.* JP 2000086627.

HMRZ-62

289772

7-[2-(2-Amino-5-chlorothiazol-4-yl)-2(*Z*)-(hydroxyimino)acetamido]-3-[2-(7-oxo-7*H*-thieno[3,2-*b*]thiopyran-5-ylsulfanyl)vinyl]-3-cephem-4-carboxylic acid



C21 H14 Cl N5 O6 S5; Mol wt: 628.1536

ACTION – Cephalosporin antibiotic with strong *in vitro* antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MIC₈₀ = 0.39 µg/ml) and vancomycin-resistant *Enterococcus faecalis* (MIC = 0.78 µg/ml). Compound was ineffective against Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*.

SOURCE – Zenyaku Kogyo.

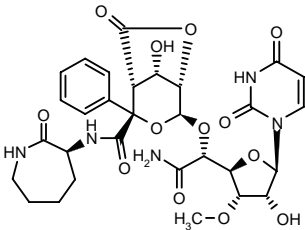
REFERENCES

1. Yamazaki, H. et al. *Novel cephalosporins 2. Synthesis of 3-heterocyclic-fused thiopyranylthiovinyl cephalosporins and antibacterial activity against methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus faecalis*. J Antibiot 2000, 53(5): 551.

ANTIBACTERIAL DRUGS

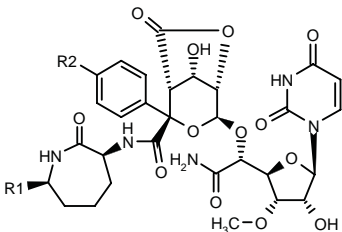
288695

(1*R*,2*S*,4*S*,5*S*,8*S*)-4-[1(*R*)-Carbamoyl-1-[(2*S*,3*S*,4*R*,5*R*)-5-[2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl]-4-hydroxy-3-methoxytetrahydrofuran-2-yl]methoxy]-8-hydroxy-7-oxo-*N*-[2-oxoperhydroazepin-3(*S*)-yl]-2-phenyl-3,6-dioxabicyclo[3.2.1]octane-2-carboxamide



C30 H35 N5 O13; Mol wt: 673.6285

ACTION – Antibacterial agent obtained from the known compound A-500359A⁺, specifically active against methicillin-resistant *Staphylococcus aureus* (MRSA). Other exemplified lactone derivatives include the following:



Compound	R1	R2	Formula
288696	H	Me	C ₃₁ H ₃₇ N ₅ O ₁₃
288697	Me	H	C ₃₁ H ₃₇ N ₅ O ₁₃

SOURCE – Sankyo.

REFERENCES

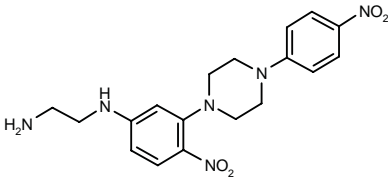
1. Hotoda, H. et al. (Sankyo Co., Ltd.) *Lactone derivs*. JP 2000072774.

*Drug Data Rep 2000, 022(04): 0348.

288920

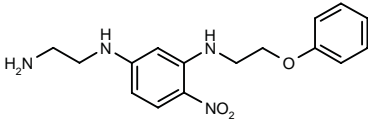
*N*¹-[4-Nitro-3-[4-(4-nitrophenyl)piperazin-1-yl]phenyl]-ethane-1,2-diamine

N-(2-Aminoethyl)-*N*-[4-nitro-3-[4-(4-nitrophenyl)piperazin-1-yl]phenyl]amine



C18 H22 N6 O4; Mol wt: 386.4098

ACTION – Antibacterial agent that acts by selectively inhibiting bacterial RNA polymerase activity, as demonstrated by IC₅₀ values of 4, 8 and 40 µg/ml, respectively, against *Staphylococcus aureus*, *Escherichia coli* and human RNA polymerase. In addition, compound exhibited MIC values of 1, 2 and 8 µg/ml, respectively, against *S. aureus*, rifampicin-resistant *S. aureus* and *E. coli*. Another specifically claimed compound from this series of aryl diamine derivatives is:



288921: C16 H20 N4 O3

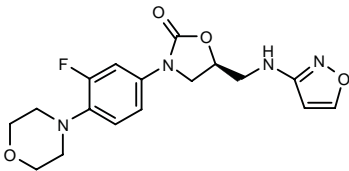
SOURCE – Scriptgen.

REFERENCES

1. Lam, K. and Xiang, Y.B. (Scriptgen Pharmaceuticals, Inc.) *Aryldiamine derivs. useful as antibacterial agents*. WO 0021539.

288969

3-[3-Fluoro-4-(4-morpholinyl)phenyl]-5(*S*)-(3-isoxazolyl-aminomethyl)oxazolidin-2-one



C17 H19 F N4 O4; Mol wt: 362.3591

ACTION – Oxazolidinone antibacterial agent found to be active against Gram-positive pathogens including methicillin- and vancomycin-resistant strains. *In vitro*, it gave respective MIC values of 0.5, 1 and 1 µg/ml against *Staphylococcus aureus* Oxford, novobiocin-resistant *S. aureus* and methicillin/quinolone-resistant *S. aureus*. Against methicillin-resistant and -sensitive strains of coagulase-negative staphylococci, compound gave respective MIC values of 0.5 and 1 µg/ml.

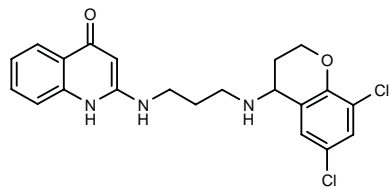
SOURCE – AstraZeneca.

REFERENCES

1. Gravestock, M.B. (AstraZeneca plc) *Heterocyclyl aminomethyloxazolidinones as antibacterials*. WO 0021960.

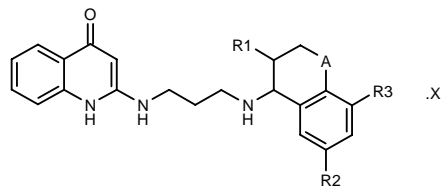
289011

2-[3-(6,8-Dichloro-3,4-dihydro-2*H*-1-benzopyran-4-ylamino)propylamino]quinolin-4(1*H*)-one

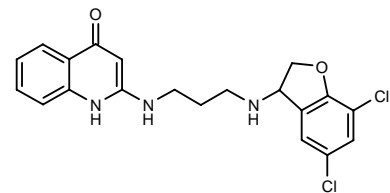


C21 H21 Cl2 N3 O2; Mol wt: 418.3219

ACTION – Antibacterial agent, a potent inhibitor of methionyl-tRNA synthetase (methionine-tRNA ligase, MRS), giving IC₅₀ values in the range < 3-100 nM against recombinant *Staphylococcus aureus* MRS; it is selective with respect to mammalian enzyme. The compound gave MIC values of 1 µg/ml or less against *S. aureus*, *Streptococcus pneumoniae* and *Enterococcus faecalis*, and in the range of 8-32 µg/ml against *Moraxella catarrhalis*. Other specifically claimed quinolones are:



Compound	R1	R2	R3	A	X	Formula
289013	H	Br	Br	NH		C ₂₁ H ₂₂ Br ₂ N ₄ O
289014	H	Cl	I	O		C ₂₁ H ₂₁ ClIN ₃ O ₂
289015	H	Cl	Br	NH		C ₂₁ H ₂₂ BrClN ₄ O
289016	H	Br	Cl	NH		C ₂₁ H ₂₂ BrClN ₄ O
289017	H	Br	Et	NH		C ₂₃ H ₂₇ BrN ₄ O
289018	H	Et	I	NH	2HCl	C ₂₃ H ₂₇ IN ₄ O.2HCl
289019	H	OMe	Br	NH		C ₂₂ H ₂₆ BrN ₄ O ₂
289020	H	I	Cl	O		C ₂₁ H ₂₁ ClIN ₃ O ₂
289021	Me	Cl	Cl	O		C ₂₂ H ₂₃ Cl ₂ N ₃ O ₂
289022	H	Br	Br	O		C ₂₁ H ₂₁ Br ₂ N ₃ O ₂



289012: C20 H19 Cl2 N3 O2

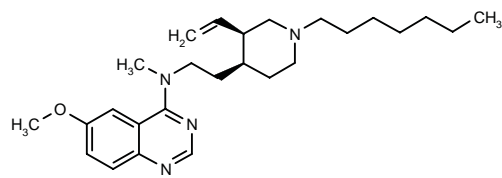
SOURCE – SmithKline Beecham.

REFERENCES

1. Berge, J.M. et al. (SmithKline Beecham plc) *Quinolones as t-RNA synthetase inhibitors and antibacterial agents*. WO 0021949.

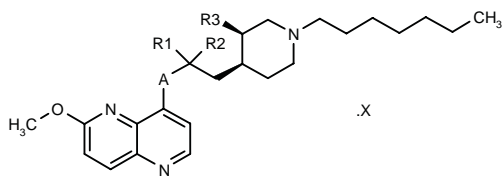
289049

N-[2-[1-Heptyl-3(*R*)-vinylpiperidin-4(*S*)-yl]ethyl]-6-methoxy-*N*-methylquinazolin-4-amine

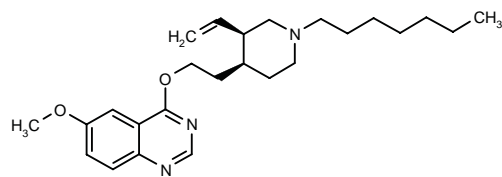


C26 H40 N4 O; Mol wt: 424.6290

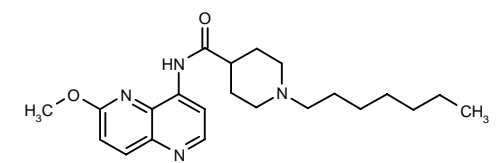
ACTION – Antibacterial agent active against both Gram-positive and Gram-negative organisms such as *Staphylococcus aureus* Oxford, *S. aureus* WCUH29, *S. aureus* Carter 37, *Enterococcus faecalis* I, *Moraxella catarrhalis* Ravasio and *Streptococcus pneumoniae* R6 (MIC = 0.5, 0.5, 0.5, 4 , 0.5 and 0.5 µg/ml, respectively). Other specifically claimed naphthyridine compounds and analogues from this series are:



Compound	R1	R2	R3	A	X	Formula
289052		-O-	vinyl	NH		C ₂₅ H ₃₆ N ₄ O ₂
289053	OH	H	vinyl	CH2		C ₂₆ H ₃₉ N ₃ O ₂
289054		-O-	CH2CONH2	NH	oxalate	C ₂₅ H ₃₇ N ₅ O ₃ .C ₂ H ₂ O ₄



289050: C25 H37 N3 O2



289051: C22 H32 N4 O2

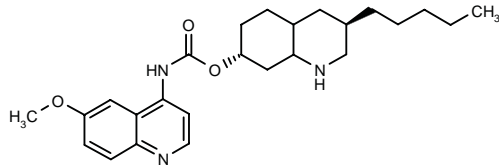
SOURCE – SmithKline Beecham.

REFERENCES

1. Hatton, I.K. and Pearson, N.D. (SmithKline Beecham plc) *Naphthyridine cpds. and their azoisosteric analogues as antibacterials*. WO 0021948.

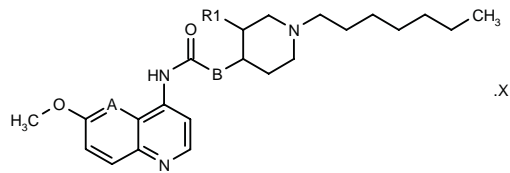
289059

N-(6-Methoxyquinolin-4-yl)carbamic acid 3(R)-pentyl-decahydroquinolin-7(R)-yl ester

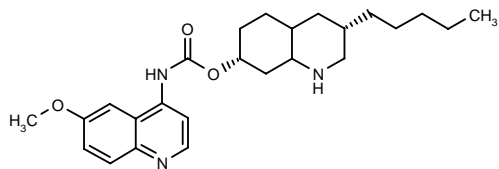


C25 H35 N3 O3; Mol wt: 425.5695

ACTION – Antibacterial agent found to be active against a wide range of bacteria including both Gram-positive and Gram-negative organisms; it may be used alone or in combination with other antibiotics or with β -lactamase inhibitors. Compound gave MIC values of 2, 4, 8, 8, 32 and 1 μ g/ml against *Staphylococcus aureus* Oxford, *S. aureus* WCUH29, *S. aureus* Carter 37, *Enterococcus faecalis* I, *Moraxella catarrhalis* Ravasio and *Streptococcus pneumoniae*, respectively. Other specifically claimed quinoline derivatives are:



Compound	R1	A	B	X	Isomer	Formula
289061	H	CH	O			C ₂₃ H ₃₃ N ₃ O ₃
289062	H	CH	NH			C ₂₃ H ₃₄ N ₄ O ₂
289063	CH ₂ OH	CH	NH	oxalate	cis	C ₂₄ H ₃₆ N ₄ O ₃ ·C ₂ H ₂ O ₄
289064	CH ₂ OH	N	NH	oxalate	cis	C ₂₃ H ₃₆ N ₅ O ₃ ·C ₂ H ₂ O ₄
289065	H	N	NH	oxalate		C ₂₂ H ₃₃ N ₅ O ₂ ·C ₂ H ₂ O ₄



289060: C25 H35 N3 O3

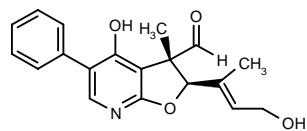
SOURCE – SmithKline Beecham.

REFERENCES

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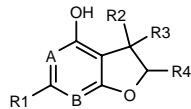
289636

(2*R**,3*R**)-4-Hydroxy-2-[3-hydroxy-1-methyl-1(*E*)-propenyl]-3-methyl-5-phenyl-2,3-dihydrofuro[2,3-*b*]pyridine-3-carbaldehyde



C19 H19 N O4; Mol wt: 325.3621

ACTION – Antibacterial agent produced by fermentation of the fungus *Cladobotryum varium* (FERM BP-5732), giving MIC values of 25, 25, 6.25, 6.25, 50 and 50 μ g/ml, respectively, against *Staphylococcus aureus* 01A1105, *Streptococcus agalactiae* 02B1023, *Streptococcus pyogenes* 02C1068, *Streptococcus pneumoniae* 02J1095, *Haemophilus influenzae* 54A0085 and *Moraxella catarrhalis* 87A1055. Other compounds from this series of furopyridine derivatives include the following:



Compound	R1	R2	R3	R4	A	B	Isomer	Formula
289637	Ph	CH ₂ OH	Me	C(Me)=CHMe	N	CH	2 <i>R</i> *,3 <i>R</i> *	C ₁₉ H ₂₁ NO ₃
289639	H	CH ₂ OH	CH ₂ OH	C(Me)=CHMe	C(Ph)	N		C ₁₉ H ₂₁ NO ₄
289640	H	CH=C(Me)-CH(OH)Me	H	OH	N	C(Ph)	2 <i>R</i> *,3 <i>S</i> *	C ₁₈ H ₁₉ NO ₄
289641	H	CH ₂ OH	Me	C(Me)=CHMe	C(Ph)	N	2 <i>R</i> *,3 <i>S</i> *	C ₁₉ H ₂₁ NO ₃

SOURCE – Pfizer.

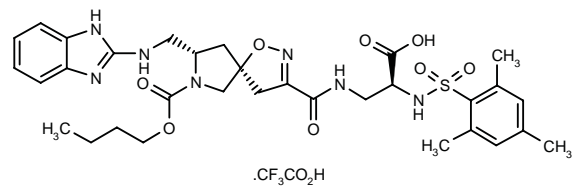
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1. Sugie, Y. et al. (Pfizer Inc.) *Fuopyridine antibacterials*. EP 0999212, JP 2000143666.

SJ-755

286496

3-[(5*S*,8*S*)-8-(1*H*-Benzimidazol-2-ylaminomethyl)-7-(butoxycarbonyl)-1-oxa-2,7-diazaspiro[4.4]non-2-en-3-ylcarboxamido]-2(*S*)-(2,4,6-trimethylphenylsulfonamido)propionic acid trifluoroacetate



C32 H41 N7 O8 S . C2 H F3 O2; Mol wt: 797.8048

ACTION – Low-molecular-weight nonpeptide antagonist of integrin $\alpha_5\beta_1$ proven to inhibit the internalization of streptococci by primary human tonsillar epithelial cells and immortalized human epithelial cells (A549), thus increasing the extent of bacterial killing by antibiotics. Compound blocked fibronectin binding by human tonsillar epithelial cells and A549 cells, but it did not affect fibronectin binding by the bacterial fibronectin-binding protein M1. Potentially useful for the treatment of infectious diseases in combination with other antimicrobials.

SOURCES – DuPont Pharmaceuticals; University of Minnesota, Minneapolis, MN (US).

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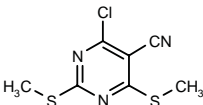
2. Jadhav, P.K. and Smallheer, J.M. (DuPont Pharmaceuticals Co.) *Spirocycle integrin inhibitors*. EP 0888344, US 5760029, WO 9733887.

3. Cue, D. et al. *A nonpeptide integrin antagonist can inhibit epithelial cell ingestion of Streptococcus pyogenes by blocking formation of integrin alpha5beta1-fibronectin-M1 protein complexes*. Proc Natl Acad Sci USA 2000, 97(6): 2858.

ANTIFUNGAL AGENTS

288880

4-Chloro-2,6-bis(methylsulfanyl)pyrimidine-5-carbonitrile



C7 H6 Cl N3 S2; Mol wt: 231.7304

ACTION – Antifungal agent, a pyrimidine derivative active against *Aspergillus fumigatus*, *Trichophyton mentagrophytes* and *Cryptococcus neoformans* (MIC = 0.002, 0.005 and 1.56 µg/ml, respectively). Compound showed activity similar to that of amphotericin B, but was much more active than ketoconazole (MIC = 0.7, 0.1 and 0.1 µg/ml, respectively).

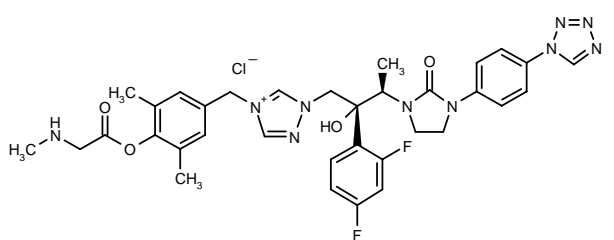
SOURCE – Central Drug Research Institute, Lucknow (IN).

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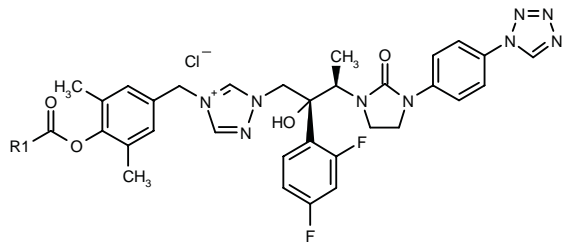
289185

1-[(2*R*,3*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-3-[2-oxo-3-[4-(1*H*-tetrazol-1-yl)phenyl]imidazolidin-1-yl]butyl]-4-[3,5-dimethyl-4-[2-(methylamino)acetoxy]benzyl]-1*H*-1,2,4-triazol-4-ium chloride



C34 H37 Cl F2 N10 O4; Mol wt: 723.1813

ACTION – Triazole antifungal agent, shown to be effective in increasing survival in mice with *Candida albicans* infection, completely preventing mortality for 4 days at 1.04 µmol/kg i.v. Other exemplified compounds are:



Compound	R1	Formula
289186	2(S)-pyrrolidinyl	C ₃₆ H ₃₉ ClF ₂ N ₁₀ O ₄
289187	(S)-CH(Me)NH2	C ₃₄ H ₃₇ ClF ₂ N ₁₀ O ₄
289188	CH2NH2	C ₃₃ H ₃₅ ClF ₂ N ₁₀ O ₄

SOURCE – Takeda.

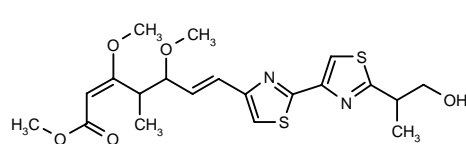
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CYSTOTHIAZOLE F

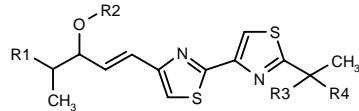
288574

3,5-Dimethoxy-4-methyl-7-[2-[2-(2-hydroxy-1-methyl-ethyl)thiazol-4-yl]thiazol-4-yl]-2(*E*),6(*E*)-heptadienoic acid methyl ester



C20 H26 N2 O5 S2; Mol wt: 438.5664

ACTION – Antifungal agent isolated from *Cystobacter fuscus* (FERM P-15997) along with the following compounds:



Compound	R1	R2	R3	R4	Formula
Cystothiazole C [288577]	(E)-C(OMe)=CHCO2Me	H	H	Me	C ₁₉ H ₂₄ N ₂ O ₄ S ₂
Cystothiazole D [288578]	(E)-C(OMe)=CHCO2Me	H	-CH2-		C ₁₈ H ₂₂ N ₂ O ₄ S ₂
Cystothiazole E [288580]	Ac	Me	H	Me	C ₁₇ H ₂₂ N ₂ O ₂ S ₂

SOURCE – Ajinomoto.

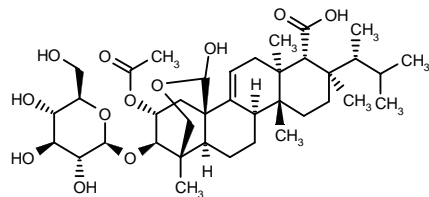
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ENFUMAFUNGIN*

254933

(1*S*,4*aR*,6*aS*,7*R*,8*R*,10*aR*,10*bR*,12*aS*,14*R*,15*R*)-14-Acetoxy-8-(1,2-dimethylpropyl)-15-(β-*D*-glucopyranosyloxy)-4-hydroxy-1,6*a*,8,10*a*-tetramethyl-1,2,6*a*,7,8,9,10,10*a*,10*b*,11,12,12*a*-dodecahydro-4*H*,6*H*-1,4*a*-propano-phenanthro[1,2-*c*]pyran-7-carboxylic acid



C38 H60 O12; Mol wt: 708.8800

ACTION – Antifungal agent, a natural acidic terpenoid that acts as a (1,3)-β-*D*-glucan synthase inhibitor (IC₅₀ = 0.05 μg/ml in *Candida albicans*) and is active against pathogenic *Candida* and *Aspergillus* strains, with MIC values ranging from < 0.03 μg/ml to 2 μg/ml. In addition to *in vitro* antifungal activity, it exhibited activity against *C. albicans* infection in animal models.

SOURCE – Merck & Co.

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1. Schwartz, R.E. et al. (Merck & Co., Inc.) *Antifungal agent*. EP 0877618, JP 2000504563, US 5756472, WO 9727860.

2. Onishi, J. et al. *Discovery of novel antifungal (1,3)-β-D-glucan synthase inhibitors*. Antimicrob Agents Chemother 2000, 44(2): 368.

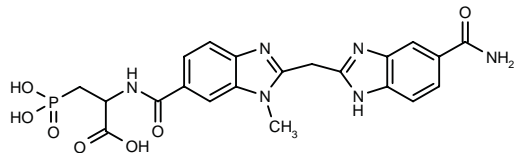
3. Schwartz, R.E. et al. *Isolation and structural determination of enfumafungin, a triterpene glycoside antifungal agent that is a specific inhibitor of glucan synthesis*. J Am Chem Soc 2000, 122(20): 4882.

*Identified compound **254933** Drug Data Rep 1997, 019(10): 0924.

ANTIVIRAL DRUGS

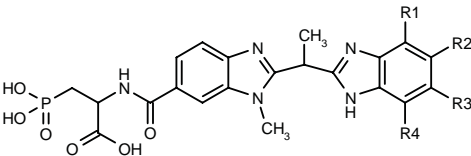
288687

2-[2-(5-Carbamoyl-1*H*-benzimidazol-2-ylmethyl)-1-methyl-1*H*-benzimidazol-6-ylcarboxamido]-3-phosphonopropionic acid

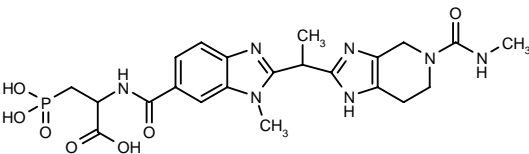


C21 H21 N6 O7 P; Mol wt: 500.4059

ACTION – Serine protease inhibitor, particularly active against hepatitis C virus (HCV) NS3 protease (K_i = 0.062 μM), for the treatment of HCV infections. Other specifically claimed biheterocyclic compounds are:



Compound	R1	R2	R3=R4	Formula
288688	H	CONH2	H	C ₂₂ H ₂₃ N ₆ O ₇ P
288691	H	H	H	C ₂₁ H ₂₂ N ₆ O ₆ P
288692	H	F	H	C ₂₁ H ₂₁ FN ₆ O ₆ P
288693	H	OH	H	C ₂₁ H ₂₂ N ₆ O ₇ P
288694	F	F	F	C ₂₁ H ₁₈ F ₄ N ₆ O ₆ P



288690: C22 H28 N7 O7 P

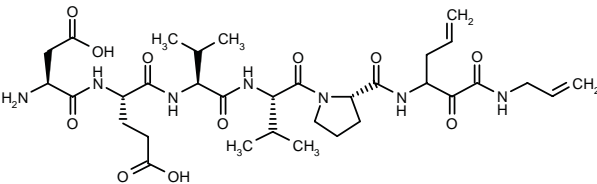
SOURCE – Axys Pharmaceuticals.

REFERENCES

1. Hataye, J.M. et al. (Axys Pharmaceuticals, Inc.) *Novel cpds. and compsns. for treating hepatitis C infections*. WO 0020400.

288883

L-Aspartyl-L-glutamyl-L-valyl-L-valyl-L-proline *N*-[1-[2-(allylamino)-2-oxoacetyl]-3-butenyl]amide



C33 H51 N7 O11; Mol wt: 721.8039

ACTION – Antiviral agent, an α-ketoamide with inhibitory activity against hepatitis C virus NS3 protease (IC₅₀ = 0.34 μM).

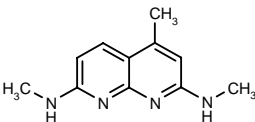
SOURCE – DuPont Pharmaceuticals.

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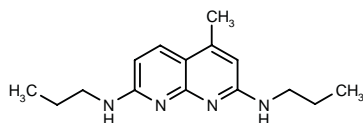
289057

*N*²,*N*⁷,4-Trimethyl[1,8]naphthyridine-2,7-diamine



C11 H14 N4; Mol wt: 202.2596

ACTION – Antiviral agent active against influenza A virus ($IC_{50} = 8.17, 23.2$ and $14 \mu\text{g/ml}$ against A/Hong Kong/68, A/Bakum/5/95 and A/Singapur/1/57, respectively, in a plaque reduction assay in MDCK cells), with a therapeutic index (CC_{50}/IC_{50}) of about 10; compound was also active against influenza B virus ($IC_{50} = 6.2 \mu\text{g/ml}$ against B/Harbin/7/94 and B/Yamanashi/166/98). Compound had no effect on cell-free virus and did not inhibit the adsorption of influenza A virus to the cell surface; rather, its mechanism of antiviral activity is based on inhibition of virus penetration into the cell, probably leading to delayed or reduced viral mRNA synthesis. Another related compound is:



289058: C₁₅ H₂₂ N₄

SOURCES – Friedrich-Schiller-Universität Jena, Jena (DE); Hans Knöll Institute for Natural Product Research, Jena (DE).

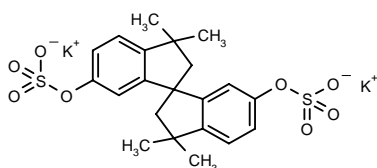
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AIDS MEDICINES

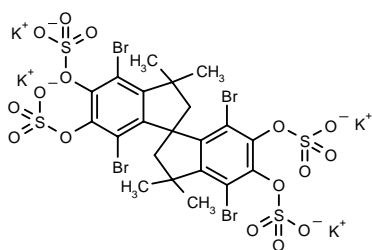
289258

3,3,3',3'-Tetramethyl-1,1'-spirobiindane-6,6'-diol disulfate dipotassium salt



C₂₁ H₂₂ K₂ O₈ S₂; Mol wt: 544.7248

ACTION – Anti-HIV agent, a selective inhibitor of HIV-1 integrase ($IC_{50} = 12$ and $54 \mu\text{M}$ in the presence of Mn^{2+} or Mg^{2+} as cofactor, respectively) with no activity against DNA topoisomerase type 1B and low cytotoxicity against HeLa cells ($IC_{50} > 400 \mu\text{M}$). Another related compound is:



289259: C₂₁ H₁₆ Br₄ K₄O₁₆ S₄

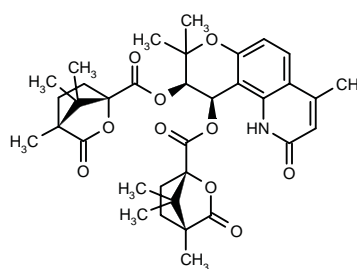
SOURCES – University of California, San Diego, La Jolla, CA (US); Salk Institute for Biological Studies, La Jolla, CA (US).

REFERENCES

1. Molteni, V. et al. *A new class of HIV-1 integrase inhibitors: The 3,3,3',3'-tetramethyl-1,1'-spirobi (indan)-5',5',6,6'-tetrol family*. *J Med Chem* 2000, 43(10): 2031.

289868

4,8,8-Trimethyl-9(*R*),10(*R*)-bis[4(*R*),7,7-trimethyl-2-oxabicyclo[2.2.1]hept-1-ylcarbonyloxy]-1,8,9,10-tetrahydro-2*H*-pyrano[2,3-*h*]quinolin-2-one



C₃₅ H₄₁ N O₁₀; Mol wt: 635.7059

M.p. 156-8 °C; $[\alpha]_D^{25} +98.0^\circ$ (*c* 0.4, *CHCl*₃).

ACTION – Anti-HIV agent, an analogue of the khellactone suksdorfin extracted from the fruit of *Lomatium suksdorfii*. Compound exhibited potent anti-HIV activity in acutely infected H9 lymphocytes, with an EC_{50} value of 0.24 nM and a therapeutic index of over 100,000, being about 225-fold more potent than zidovudine in this assay. Mechanism of action studies are in progress.

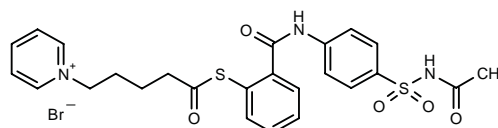
SOURCES – Biotech Research Laboratories; University of North Carolina, Chapel Hill, NC (US).

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290057

1-[5-[2-[*N*-[4-(Acetamididosulfonyl)phenyl]carbamoyl]-phenylsulfanyl]-5-oxopentyl]pyridinium bromide



C₂₅ H₂₆ Br N₃ O₅ S₂; Mol wt: 592.5324

ACTION – Anti-HIV agent, a pyridinioalkanoyl thioester that targets HIV-1 nucleocapsid p7 protein (NCp7) zinc fingers. Compound exhibited good antiviral activity in HIV-1-infected CEM-SS cells ($EC_{50} = 6.2 \mu\text{M}$) and low cytotoxicity in uninfected cells ($IC_{50} > 316 \mu\text{M}$). Potentially useful as a treatment for HIV-1 infection and for preventing HIV-1 transmission.

SOURCES – Achillion; National Institutes of Health, Bethesda, MD (US).

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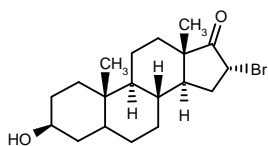
HE-2000

272206

16 α -Bromoepiandrosterone

(3*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*R*)-16-Bromo-3-hydroxy-10,13-dimethylhexadecahydro-17*H*-cyclopenta[*a*]-phenanthren-17-one

Inactivin™



C19 H29 Br O2; Mol wt: 369.3401

ACTION – Anti-HIV agent that exerts both antiviral and immunomodulating activity. It may target HIV-disturbed metabolic pathways in cells via its ability to bind to glucose-6-phosphate dehydrogenase and it also appears to induce a Th2-to-Th1 shift. In macaques infected with the highly pathogenic genetically combined SIV/HIV virus SHIV 229, compound increased the CD4+ cell count and the average survival time to > 1 year. Preliminary results from a phase I/II clinical trial in HIV-infected patients indicated that HE-2000 was well tolerated, with no drug-related serious adverse events. In these patients, it appeared to restore the immune system balance by shifting the cytokine pattern from a Th2 status back to a Th1 state, leading to activation of a number of cell types potentially important for fighting infection such as T-cells, LAK cells, natural killer (NK) cells and dendritic cells. Compound is currently undergoing phase I/II clinical trials for the treatment of malaria and clinical studies are also planned in hepatitis C.

SOURCES – Colthurst; Hollis-Eden.

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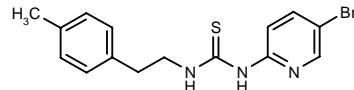
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3. du Plooy, W.J. et al. *Bromine epiandrosterone (Inactivin) as immunomodulator in patients with HIV/AIDS*. 7th World Conf Clin Pharmacol Ther (July 15-20, Florence) 2000, Abst 1013.
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11. *Hollis-Eden initiates phase I/II AIDS trial, reports preclinical results*. DailyDrugNews.com (Daily Essentials) 1999, May 12.
12. *Hollis-Eden reports preliminary results from phase I/II HIV trial in South Africa*. DailyDrugNews.com (Daily Essentials) 1999, Dec 7.
13. *Hollis-Eden to initiate HIV/AIDS trials with HE-2000 in South Africa*. DailyDrugNews.com (Daily Essentials) 1999, March 15.
14. *Hollis-Eden updates progress of HE-2000 clinical trials*. DailyDrugNews.com (Daily Essentials) 1999, Sept 13.
15. *Initial clinical results with HE-2000 indicate immune system switch in HIV*. DailyDrugNews.com (Daily Essentials) 2000, April 20.
16. *Novel AIDS therapeutic enters phase I/II testing in South Africa*. DailyDrugNews.com (Daily Essentials) 1998, Sept 29.
17. *Novel therapy for HIV/AIDS to enter clinical trials in the U.S*. DailyDrugNews.com (Daily Essentials) 1999, March 2.

HI-244

288279

N-(5-Bromopyridin-2-yl)-*N'*-[2-(4-methylphenyl)ethyl]-thiourea



C15 H16 Br N3 S; Mol wt: 350.2824

M.p. 159-60 °C.

ACTION – Anti-HIV agent, an inhibitor of HIV-1 reverse transcriptase (IC₅₀ = 0.4 μM) proven to inhibit HIV-1 replication in peripheral blood mononuclear cells (PBMCs) with an IC₅₀ value of 7 nM, equal to that of trovirdine. However, compound was 20-fold more effective than trovirdine against the multidrug-resistant HIV-1 strain RT-MDR with a V106A mutation and 7-fold more potent against the non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistant HIV-1 strain A17 with a Y181C mutation (IC₅₀ < 0.001 and 0.07 μM, respectively, for compound vs. 0.02 and 0.5 μM, respectively, for trovirdine). It showed low cytotoxicity against uninfected PBMCs (CC₅₀ = 71 μM).

SOURCE – Parker Hughes Institute, Roseville, MN (US).

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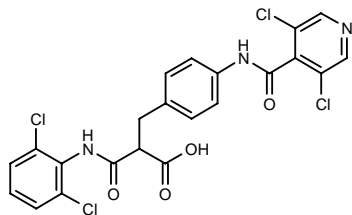
1. Uckun, F.M. et al. *N-[2-(4-Methylphenyl)ethyl]-N'-[2-(5-bromopyridyl)]thiourea as a potent inhibitor of NNRTI-resistant and multidrug-resistant human immunodeficiency virus type 1*. Antivir Chem Chemother 2000, 11(2): 135.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

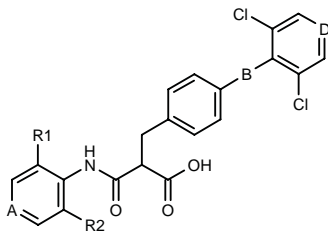
288766

3-(2,6-Dichlorophenylamino)-2-[4-(3,5-dichloropyridin-4-ylcarboxamido)benzyl]-3-oxopropionic acid



C22 H15 Cl4 N3 O4; Mol wt: 527.1895

ACTION – Integrin inhibitor that selectively inhibits the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ and modulates cell adhesion. The compound is reported to be particularly useful for the treatment of immune and inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, allograft rejection, diabetes, dermatitis, asthma and inflammatory bowel disease. Other specifically claimed phenylalkanoic acid derivatives are:



Compound	R1=R2	A	B	D	Formula
288768	OMe	CH	-NHCO-	N	C ₂₄ H ₂₁ Cl ₂ N ₃ O ₆
288769	Me	N	-NHCO-	N	C ₂₃ H ₂₀ Cl ₂ N ₄ O ₄
288770	Ome	CH	-NHCO-	CH	C ₂₆ H ₂₂ Cl ₂ N ₂ O ₆
288771	Ome	CH	-OCH2-	CH	C ₂₆ H ₂₃ Cl ₂ NO ₆

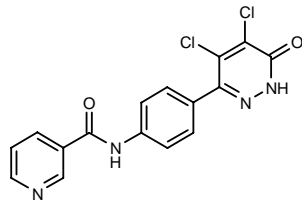
SOURCE – Celltech Group.

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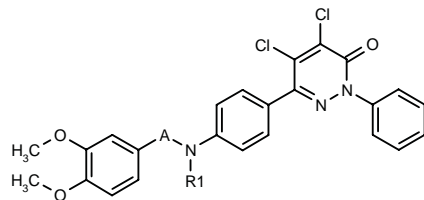
288910

N-[4-(4,5-Dichloro-6-oxo-1,6-dihydropyridazin-3-yl)phen-yl]pyridine-3-carboxamide



C16 H10 Cl2 N4 O2; Mol wt: 361.1870

ACTION – Cell adhesion inhibitor shown to produce 100% inhibition of ICAM-1 expression in a cell adhesion assay using TNF- α -stimulated human umbilical vein endothelial cells (HUVEC). Other exemplified pyridazinone derivatives include the following:



Compound	R1	A	Formula
288911	H	-CO-	C ₂₅ H ₁₉ Cl ₂ N ₃ O ₄
288912	H	-CH2CO-	C ₂₆ H ₂₁ Cl ₂ N ₃ O ₄
288913	Ac	-CH2-	C ₂₇ H ₂₃ Cl ₂ N ₃ O ₄

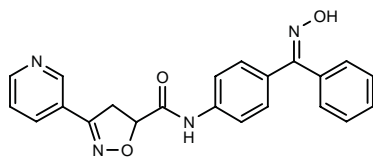
SOURCE – Nihon Nohyaku.

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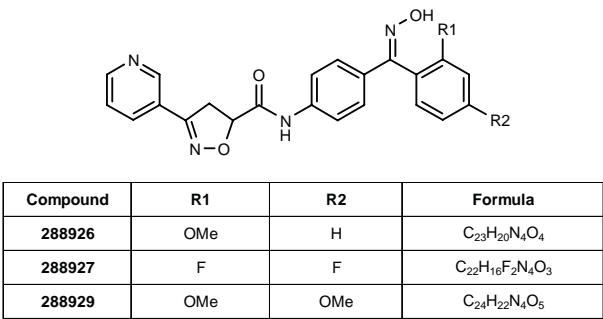
288925

N-[4-[1-(Hydroxyimino)-1-(phenyl)methyl]phenyl]-3-(3-pyridyl)-4,5-dihydroisoxazole-5-carboxamide



C22 H18 N4 O3; Mol wt: 386.4092

ACTION – Immunomodulating agent and cell proliferation inhibitor, particularly useful for the treatment of T-cell-mediated diseases such as rheumatoid arthritis, juvenile arthritis and osteoarthritis, systemic inflammatory diseases such as systemic lupus erythematosus, psoriasis, T-cell leukemia, transplant rejection and graft-versus-host disease. Compound gave 86% inhibition of T-cell blast formation in human whole blood at 0.1 μ M. A representative compound from a series of 4,5-dihydroisoxazole derivatives, wherein the following are also included:



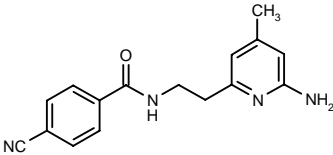
SOURCE – Janssen.

REFERENCES

1. Freyne, E.J.E. et al. (Janssen Pharmaceutica NV) *4,5-Dihydro-isoxazole derivs. and their pharmaceutical use.* WO 0021959.

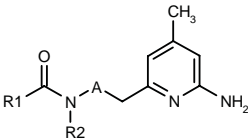
288950

N-[2-(6-Amino-4-methylpyridin-2-yl)ethyl]-4-cyanobenzamide

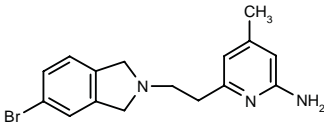


C16 H16 N4 O; Mol wt: 280.3294

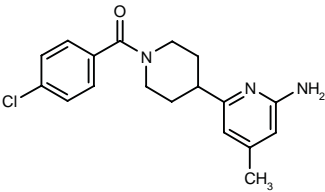
ACTION- Antiinflammatory agent that acts by inhibiting the inducible form of the enzyme nitric oxide synthase (iNOS; IC₅₀ < 25 μM), particularly useful for the treatment of inflammation and pain, alone or in combination with cyclooxygenase type 2 (COX-2) inhibitors such as celecoxib or MK-966. Other specifically claimed compounds are:



Compound	R1	R2	A	Formula
288953	4-CN-Ph	H	-(CH2)3-	C ₁₈ H ₂₀ N ₄ O
288955	4-Cl-Ph	H	-CH2-	C ₁₅ H ₁₆ ClN ₃ O
288959	4-CN-Ph	Me	-CH2-	C ₁₇ H ₁₈ N ₄ O
288960	2-furyl	Me	-CH2-	C ₁₄ H ₁₇ N ₃ O ₂
288962	4-Cl-Ph	Me	-CH2-	C ₁₆ H ₁₈ ClN ₃ O
288963	4-Cl-Ph	H	-(CH2)2-	C ₁₆ H ₁₈ ClN ₃ O



288957: C16 H18 Br N3



288964: C18 H20 Cl N3 O

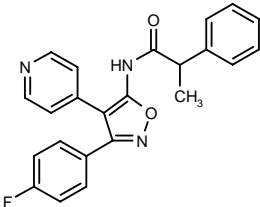
SOURCE – AstraZeneca.

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1. Connolly, S. and Cox, D. (AstraZeneca U.K., Ltd.; AstraZeneca AB) *Compounds.* WO 0021934.

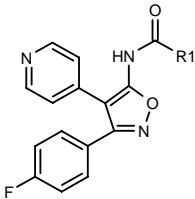
289181

N-[3-(4-Fluorophenyl)-4-(4-pyridinyl)isoxazol-5-yl]-2-phenylpropionamide



C23 H18 F N3 O2; Mol wt: 387.4122

ACTION – p38 MAP kinase inhibitor (IC₅₀ = 0.020 nM in THP-1 cells) that inhibits the production of cytokines such as IL-1, IL-6 and TNF-α. A representative compound from a series of 5-aminoisoxazole derivatives, wherein the following are also included:



Compound	R1	Formula
289182	CH2Ph	C ₂₂ H ₁₆ FN ₃ O ₂
289183	4-MeO-PhCH2	C ₂₃ H ₁₈ FN ₃ O ₃
289184	3-thienyl	C ₁₉ H ₁₂ FN ₃ O ₂ S

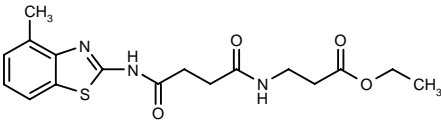
SOURCE – Teikoku Hormone.

REFERENCES

1. Minami, N. et al. (Teikoku Hormone Manufacturing Co., Ltd.) *5-Aminoisoxazole derivs.* JP 2000086657.

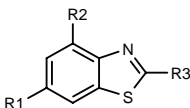
289218

3-[4-(4-Methylbenzothiazol-2-ylamino)-4-oxobutyr-amido]-propionic acid ethyl ester



C17 H21 N3 O4 S; Mol wt: 363.4359

ACTION – Cell adhesion inhibitor shown to produce 100% inhibition of cell adhesion using IL-1β-stimulated human umbilical vein endothelial cells (HUVEC) and U937 cells at a concentration of 50 μM. The compound is expected to be useful as an immunosuppressant, antiinflammatory, antiallergic and antimetastatic agent. Other exemplified compounds from this series of 2-substituted benzothiazole derivatives include the following:



Compound	R1	R2	R3	Formula
289219	Me	H	NHCOCH2CH2CONHCH2CH2CO2Et	C ₁₇ H ₂₁ N ₃ O ₄ S
289220	Me	H	NHCOCH2CONH(CH2)3CO2Et	C ₁₇ H ₂₁ N ₃ O ₄ S
289221	Me	H	NHCOCH2CH2CONH(CH2)3CO2Et	C ₁₈ H ₂₃ N ₃ O ₄ S
289222	Et	H	NHCOCH2CH2CONHCH2CH2CO2Et	C ₁₈ H ₂₃ N ₃ O ₄ S
289223	H	Me	SO2(CH2)3CONHCH2CH2CO2Et	C ₁₇ H ₂₂ N ₂ O ₅ S ₂
289224	Me	H	SO(CH2)3CONHCH2CH2CO2Et	C ₁₇ H ₂₂ N ₂ O ₄ S ₂

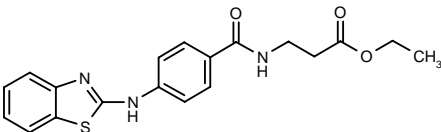
SOURCE – Kyorin.

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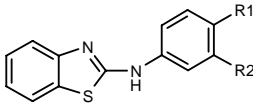
289225

3-[4-(2-Benzothiazolylamino)benzamido]propionic acid ethyl ester



C19 H19 N3 O3 S; Mol wt: 369.4431

ACTION – Cell adhesion inhibitor proven to produce 100% inhibition of cell adhesion using IL-1β-stimulated human umbilical vein endothelial cells (HUVEC) and U937 cells at a concentration of 50 μM. The compound is expected to be useful as an immunosuppressant, antiinflammatory, antiallergic and antimetastatic agent. Other exemplified compounds from this series of 2-substituted benzothiazole derivatives include the following:



Compound	R1	R2	Formula
289226	CH2CONHCH2CH2CO2Et	H	C ₂₀ H ₂₁ N ₃ O ₃ S
289227	CH2CONH(CH2)3CO2Et	H	C ₂₁ H ₂₃ N ₃ O ₃ S
289228	CH2CH2CONHCH2CH2CO2Et	H	C ₂₀ H ₂₁ N ₃ O ₃ S
289229	CH2CH2CONHCH2CH2CO2Et	H	C ₂₁ H ₂₃ N ₃ O ₃ S
289230	CH=CHCONHCH2CH2CO2Et	H	C ₂₁ H ₂₁ N ₃ O ₃ S
289231	H	CH2CONHCH2-CH2CO2Et	C ₂₀ H ₂₁ N ₃ O ₃ S
289232	H	CH2CONH-(CH2)3CO2Et	C ₂₁ H ₂₃ N ₃ O ₃ S
289233	CH2CONH-CH(CO2Et)CH2CO2Et	H	C ₂₃ H ₂₅ N ₃ O ₅ S
289234	OCH2CONH-CH(CO2Et)CH2CO2Et	H	C ₂₃ H ₂₅ N ₃ O ₆ S
289235	4-OH-PhCH2-CH(CO2Et)NHCOCH2O	OMe	C ₂₇ H ₂₇ N ₃ O ₆ S
289236	OCH2CONH-CH(CO2Et)CH2CO2Et	OMe	C ₂₄ H ₂₇ N ₃ O ₇ S
289237	4-(CO2-t-Bu)-1-Piz-COCH2	H	C ₂₄ H ₂₈ N ₄ O ₃ S

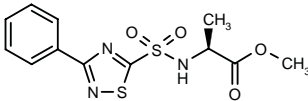
SOURCE – Kyorin.

REFERENCES

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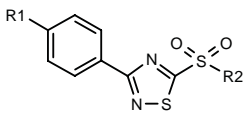
289312

2(S)-(3-Phenyl-1,2,4-thiadiazol-5-ylsulfonyl)-L-alanine methyl ester



C12 H13 N3 O4 S2; Mol wt: 327.3837

ACTION – IL-1β production inhibitor, as demonstrated by an IC₅₀ value of 2 μM for inhibition of IL-1β production in lipopolysaccharide-stimulated human mononuclear cells, with potential for the treatment of conditions associated with increased IL-1β levels such as septic shock, leukemia, hepatitis, amyotrophy, HIV infection, degenerative joint disorders, conjunctive tissue conditions, wound healing disorders and bone metabolism disorders. Other compounds from this series of thiadiazolsulfon-amides include the following:



Compound	R1	R2	Formula
289313	H	4-CO2H-cyclohexyl-CH2NH	C ₁₆ H ₁₉ N ₃ O ₄ S ₂
289314	H	4-(CO2Et)-1-Pip	C ₁₆ H ₁₉ N ₃ O ₄ S ₂
289315	H	4-oxo-1-Pip	C ₁₃ H ₁₃ N ₃ O ₃ S ₂
289316	H	4-CO2H-1-Pip	C ₁₄ H ₁₅ N ₃ O ₄ S ₂
289317	H	4-Ac-1-Piz	C ₁₄ H ₁₆ N ₄ O ₃ S ₂
289318	Cl	4-Me-1-Piz	C ₁₃ H ₁₅ ClN ₄ O ₂ S ₂

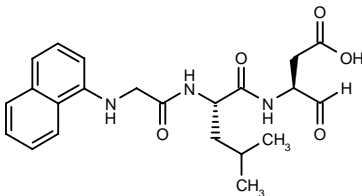
SOURCE – Aventis Pharma.

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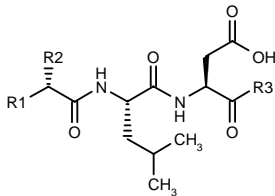
289324

N-(1-Naphthyl)-glycyl-L-leucyl-L-aspartic 1-aldehyde

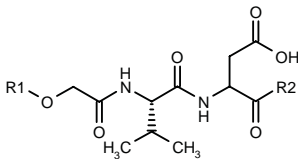


C22 H27 N3 O5; Mol wt: 413.4713

ACTION – Agent for the treatment of inflammatory, autoimmune and neurodegenerative disorders, as well as for the prevention of ischemic injury and for the preservation of organs for tranplantation, an inhibitor of IL-1β-converting enzyme (ICE; IC₅₀ = 0.033 μM) and related cysteine proteases such as CPP32 (IC₅₀ = 0.013 μM), MCH-2 (IC₅₀ = 0.037 μM), MCH-3 (IC₅₀ = 1.32 μM) and MCH-5 (IC₅₀ = 0.0076 μM). Other compounds from this series of substituted acyl dipeptides include the following:



Compound	R1	R2	R3	Formula
289325	1-Naph-NH	CH2CH2CO2H	H	C ₂₅ H ₃₁ N ₃ O ₇
289330	2-CO2H-1-Naph-O	H	CH2OPO(Ph)2	C ₃₆ H ₃₇ N ₂ O ₁₀ P



Compound	R1	R2	Isomer	Formula
289326	1-Naph	CH2F	DL	C ₂₂ H ₂₅ FN ₂ O ₆
289327	1-Naph	CH2O-PO(Ph)C6H11	L	C ₃₄ H ₄₃ N ₂ O ₈ P
289329	2-Ph-Ph	2,6-(Cl)2-Ph-CO2CH2	L	C ₃₁ H ₃₀ Cl ₂ N ₂ O ₈

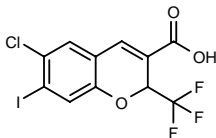
SOURCE – Idun Pharmaceuticals.

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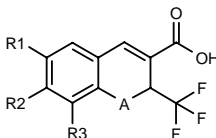
289422

6-Chloro-7-iodo-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid



C11 H5 Cl F3 I O3; Mol wt: 404.5045

ACTION – Cyclooxygenase type 2 (COX-2) inhibitor for the treatment of inflammation and related disorders. It was evaluated *in vitro* for COX-1 and COX-2 inhibition using recombinant enzymes, giving IC₅₀ values of < 0.1 and > 100 μM, respectively. It was also found to be effective *in vivo* in inhibiting paw edema formation in carrageenan-treated rats. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	Formula
289423	Cl	H	Cl	O	C ₁₁ H ₅ Cl ₂ F ₃ O ₃
289424	Me	H	Cl	O	C ₁₂ H ₈ ClF ₃ O ₃
289426	Cl	H	Cl	NH	C ₁₁ H ₆ Cl ₂ F ₃ NO ₂
289427	Cl	OPh	H	O	C ₁₇ H ₁₀ ClF ₃ O ₄
289429	Cl	4-CN-PhO	H	O	C ₁₈ H ₆ ClF ₃ NO ₄

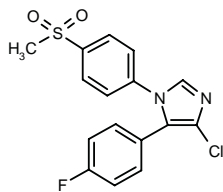
SOURCE – Pharmacia.

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1. Carter, J.S. et al. (Pharmacia Corp.) *Substd. benzopyran analogs for the treatment of inflammation*. WO 0023433.

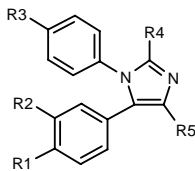
289432

4-Chloro-5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole



C16 H12 Cl F N2 O2 S; Mol wt: 350.7998

ACTION – Antiinflammatory agent that acts by potently and selectively inhibiting cyclooxygenase type 2 (COX-2), giving 89% inhibition of COX-2 at 1 μM versus 37.8% inhibition of COX-1 at 10 μM when tested in heparinized human blood. Potentially useful in the treatment of inflammation, pain, fever, dysmenorrhea, premature labor, asthma, bronchitis and cancer, particularly colon cancer. Other exemplified imidazoles include the following:



Compound	R1	R2	R3	R4	R5	Formula
289433	OEt	H	SO2Me	H	Cl	C ₁₈ H ₁₇ ClN ₂ O ₃ S
289434	Me	F	SO2Me	H	Cl	C ₁₇ H ₁₄ ClF ₂ O ₂ S
289435	F	H	SO2Me	H	Br	C ₁₆ H ₁₂ BrFN ₂ O ₂ S
289436	SO2Me	H	F	Cl	H	C ₁₆ H ₁₂ ClFN ₂ O ₂ S
289437	SO2Me	H	F	CN	H	C ₁₇ H ₁₂ FN ₃ O ₂ S
289438	SO2Me	H	Me	Cl	H	C ₁₇ H ₁₅ ClN ₂ O ₂ S
289439	Me	H	SO2NH2	H	Cl	C ₁₆ H ₁₄ ClN ₃ O ₂ S

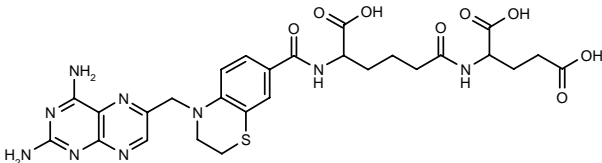
SOURCE – Uriach.

REFERENCES

1. Almansa, C. et al. (J. Uriach & Cía., SA) *Novel imidazoles with anti-inflammatory activity*. WO 0023426.

289509

N-[5-Carboxy-5-[4-(2,4-diaminopteridin-6-ylmethyl)-3,4-dihydro-2*H*-1,4-benzothiazin-7-ylcarboxamido]pentanoyl]-DL-glutamic acid



C27 H31 N9 O8 S; Mol wt: 641.6629

ACTION – Dihydrofolate reductase (DHFR) inhibitor (IC₅₀ = 1.66 nM) potentially useful for the treatment of rheumatism. A representative compound from a series of methotrexate derivatives.

SOURCE – Chugai.

REFERENCES

1. Matsuoka, K. and Takahashi, H. (Chugai Pharmaceutical Co. Ltd.) *Mono-glutamined methotrexate derivs*. JP 2000109482.

ISIS-104838

288800

20-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is: 5'-GCTGATTAGAGAGAGGTC-3', in which the central ten nucleotides are 2'-deoxynucleotides, the last five nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethyl nucleotides and the cytidines in positions 2, 18, 19 and 20 are 2'-*O*-methoxyethyl-5'-methylcytidines

ACTION – A chimeric (deoxy gapped) antisense phosphorothioate oligonucleotide inhibitor of TNF-α expression currently undergoing preclinical evaluation for inflammatory disorders such as rheumatoid arthritis and Crohn's disease. It produced 82.0% inhibition of human TNF-α mRNA expression at 300 nM in NeoHK cells. Oral and i.v. formulations are being developed.

SOURCES – Elan; Isis Pharmaceuticals.

REFERENCES

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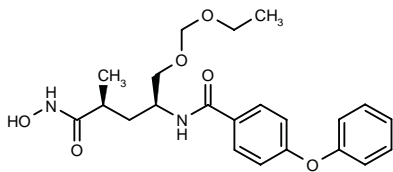
3. *New oral antisense inhibitor of TNF-alpha emerges from Isis/Elan collaboration*. DailyDrugNews.com (Daily Essentials) 2000, May 22.

4. *Pipeline*. Isis Pharmaceuticals Product Pipeline 2000, May 18.

ONO-4817*

276757

N-[1(*S*)-(Ethoxymethoxymethyl)-4-(hydroxyamino)-3(*S*)-methyl-4-oxobutyl]-4-phenoxybenzamide



C22 H28 N2 O6; Mol wt: 416.4712

ACTION – Orally active, broad-spectrum matrix metalloproteinase (MMP) inhibitor with K_i values of 0.73, 42, 1.1, 2.1, 0.45 and 1.1 nM against gelatinase A (MMP-2), stromelysin 1 (MMP-3), neutrophil collagenase (MMP-8), gelatinase B (MMP-9), macrophage elastase (MMP-12) and collagenase 3 (MMP-13), respectively; it was less active against matrilysin (MMP-7; K_i = 2500 nM) and interstitial collagenase (MMP-1; K_i = 1600 nM) and it did not inhibit other proteases such as serine proteases. In a guinea pig acute arthritis model, compound given orally at doses of 10-100 mg/kg dose-dependently inhibited lipopolysaccharide-induced proteoglycan release in the knee joints. Potentially useful for the treatment of MMP-related diseases including arthritis.

SOURCE – Ono.

REFERENCES

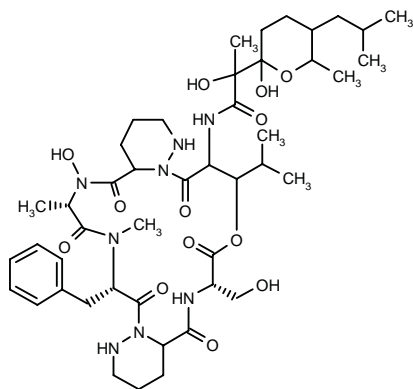
1. Takahashi, K. and Sugiura, T. (Ono Pharmaceutical Co., Ltd.) *Aminobutanoic acid derivs.* WO 9919296.
2. Yamada, A. et al. *ONO-4817, an orally active matrix metalloproteinase inhibitor, prevents lipopolysaccharide-induced proteoglycan release from the joint cartilage in guinea pigs.* *Inflamm Res* 2000, 49(4): 144.

*Identified compound **276757** Drug Data Rep 1999, 021(07): 0650.

SEK-1005

235406

(7*S*,10*S*,19*S*)-10-Benzyl-6-hydroxy-23-[2-hydroxy-(2-hydroxy-5-isobutyl-6-methyltetrahydropyran-2-yl)-propionamido]-19-(hydroxymethyl)-22-isopropyl-7,9-dimethyldocosahydro-13*H*,22*H*-dipyridazino[6,1-*f*,6',1'-*o*]-[1,4,7,10,13,16]oxapentaazacyclononadecine-5,8,11,17,20,24-hexaone



C45 H70 N8 O13; Mol wt: 931.0910

ACTION – Nonsteroidal antiinflammatory agent with steroid-like effects, a cyclic peptide isolated from *Streptomyces nobilis*, proven to protect rats against the passive Arthus reaction and carrageenan-induced edema. In addition, both SEK-1005 and prednisolone were shown to protect rats against adjuvant-induced arthritis, but compound exhibited lower toxicity than prednisolone. Its effects are postulated to be due to an increase in endogenous antiinflammatory protein synthesis.

SOURCE – Sekisui.

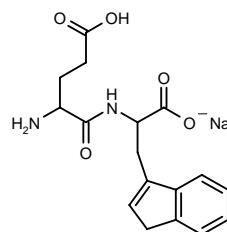
REFERENCES

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2. Akamine, T. and Inagaki, T. (Sekisui Chemical Co., Ltd.) *Therapeutic agents for wound.* JP 1999080020.
3. Fujiwara, A. and Abe, Y. (Sekisui Chemical Co., Ltd.) *Preparation method of novel peptide.* JP 1998175996.
4. Fujiwara, A. and Abe, Y. (Sekisui Chemical Co., Ltd.) *Therapeutic agents for wound.* JP 1998120575.
5. Fujiwara, A. et al. (Sekisui Chemical Co., Ltd.) *Novel peptide and therapeutic agent.* EP 0792886, JP 1996119992, JP 1996119993, JP 1996176189, JP 1996231590, JP 1997176188, US 5858971, WO 9612732.
6. Inagaki, T. (Sekisui Chemical Co., Ltd.) *Therapeutic cpds. for iron hyper-load induced disease, and therapeutic agents for it.* JP 1998194985.
7. Inagaki, T. et al. (Sekisui Chemical Co., Ltd.) *Cpds. for the treatment of peptic ulcer and agents for the treatment of peptic ulcer.* JP 2000072689.
8. Inagaki, T. et al. (Sekisui Chemical Co., Ltd.) *Preventive and therapeutic agents for periodontal disease.* JP 1998330282.
9. Niimura, K. and Abe, Y. (Sekisui Chemical Co., Ltd.) *Agents for promoting wound healing.* JP 1998259134.
10. Niimura, K. and Fujiwara, A. (Sekisui Chemical Co., Ltd.) *External agents for the treatment of parasitic dermatopathy.* JP 1998120590.
11. Watanabe, M. et al. (Sekisui Chemical Co., Ltd.) *External agents for the treatment of dermatopathy.* JP 1998259141.
12. Abe, Y. et al. *A new type antiinflammatory agent derived from a Streptomyces.* *Jpn J Pharmacol* 1995, 67(Suppl. 1): Abst P3-143.
13. Abe, Y. et al. *A novel antiinflammatory peptide derived from a Streptomyces.* *Jpn J Pharmacol* 1996, 71(Suppl. 1): Abst P-977.
14. Abe, Y. et al. *Wound healing acceleration of a novel peptide SEK-1005 isolated from Streptomyces.* *Jpn J Pharmacol* 2000, 82(Suppl. 1): Abst P-620.
15. Kuriyama, K. et al. *Anti-inflammatory action of a novel peptide, SEK-1005, isolated from a Streptomyces.* *Eur J Pharmacol* 2000, 390(1-2): 223.

IMMUNOMODULATING AGENTS

289180

2-(2-Amino-4-carboxybutyramido)-3-(1*H*-inden-3-yl)-propionic acid sodium salt



C17 H19 N2 Na O5; Mol wt: 354.3361

ACTION – Orally active, broad-spectrum matrix metalloproteinase (MMP) inhibitor with K_i values of 0.73, 42, 1.1, 2.1, 0.45 and 1.1 nM against gelatinase A (MMP-2), stromelysin 1 (MMP-3), neutrophil collagenase (MMP-8), gelatinase B (MMP-9), macrophage elastase (MMP-12) and collagenase 3 (MMP-13), respectively; it was less active against matrilysin (MMP-7; $K_i = 2500$ nM) and interstitial collagenase (MMP-1; $K_i = 1600$ nM) and it did not inhibit other proteases such as serine proteases. In a guinea pig acute arthritis model, compound given orally at doses of 10-100 mg/kg dose-dependently inhibited lipopolysaccharide-induced proteoglycan release in the knee joints. Potentially useful for the treatment of MMP-related diseases including arthritis.

SOURCE – Ono.

REFERENCES

1. Takahashi, K. and Sugiura, T. (Ono Pharmaceutical Co., Ltd.) *Aminobutanoic acid derivs.* WO 9919296.

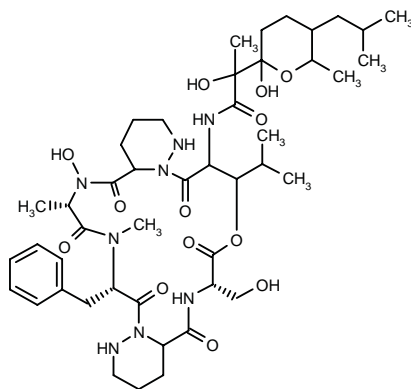
2. Yamada, A. et al. *ONO-4817, an orally active matrix metalloproteinase inhibitor, prevents lipopolysaccharide-induced proteoglycan release from the joint cartilage in guinea pigs.* *Inflamm Res* 2000, 49(4): 144.

*Identified compound **276757** Drug Data Rep 1999, 021(07): 0650.

SEK-1005

235406

(7*S*,10*S*,19*S*)-10-Benzyl-6-hydroxy-23-[2-hydroxy-(2-hydroxy-5-isobutyl-6-methyltetrahydropyran-2-yl)-propionamido]-19-(hydroxymethyl)-22-isopropyl-7,9-dimethyldocosahydro-13*H*,22*H*-dipyridazino[6,1-*f*,6',1'-*o*]-[1,4,7,10,13,16]oxapentaazacyclononadecine-5,8,11,17,20,24-hexaone



C45 H70 N8 O13; Mol wt: 931.0910

ACTION – Nonsteroidal antiinflammatory agent with steroid-like effects, a cyclic peptide isolated from *Streptomyces nobilis*, proven to protect rats against the passive Arthus reaction and carrageenan-induced edema. In addition, both SEK-1005 and prednisolone were shown to protect rats against adjuvant-induced arthritis, but compound exhibited lower toxicity than prednisolone. Its effects are postulated to be due to an increase in endogenous antiinflammatory protein synthesis.

SOURCE – Sekisui.

REFERENCES

1. Abe, Y. et al. (Sekisui Chemical Co., Ltd.) *Therapeutic agents for wound.* JP 1998338644.

2. Akamine, T. and Inagaki, T. (Sekisui Chemical Co., Ltd.) *Therapeutic agents for wound.* JP 1999080020.

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4. Fujiwara, A. and Abe, Y. (Sekisui Chemical Co., Ltd.) *Therapeutic agents for wound.* JP 1998120575.

5. Fujiwara, A. et al. (Sekisui Chemical Co., Ltd.) *Novel peptide and therapeutic agent.* EP 0792886, JP 1996119992, JP 1996119993, JP 1996176189, JP 1996231590, JP 1997176188, US 5858971, WO 9612732.

6. Inagaki, T. (Sekisui Chemical Co., Ltd.) *Therapeutic cpds. for iron hyper-load induced disease, and therapeutic agents for it.* JP 1998194985.

7. Inagaki, T. et al. (Sekisui Chemical Co., Ltd.) *Cpds. for the treatment of peptic ulcer and agents for the treatment of peptic ulcer.* JP 2000072689.

8. Inagaki, T. et al. (Sekisui Chemical Co., Ltd.) *Preventive and therapeutic agents for periodontal disease.* JP 1998330282.

9. Niimura, K. and Abe, Y. (Sekisui Chemical Co., Ltd.) *Agents for promoting wound healing.* JP 1998259134.

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11. Watanabe, M. et al. (Sekisui Chemical Co., Ltd.) *External agents for the treatment of dermatopathy.* JP 1998259141.

12. Abe, Y. et al. *A new type antiinflammatory agent derived from a Streptomyces.* *Jpn J Pharmacol* 1995, 67(Suppl. 1): Abst P3-143.

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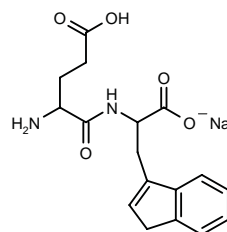
14. Abe, Y. et al. *Wound healing acceleration of a novel peptide SEK-1005 isolated from Streptomyces.* *Jpn J Pharmacol* 2000, 82(Suppl. 1): Abst P-620.

15. Kuriyama, K. et al. *Anti-inflammatory action of a novel peptide, SEK-1005, isolated from a Streptomyces.* *Eur J Pharmacol* 2000, 390(1-2): 223.

IMMUNOMODULATING AGENTS

289180

2-(2-Amino-4-carboxybutyramido)-3-(1*H*-inden-3-yl)-propionic acid sodium salt



C17 H19 N2 Na O5; Mol wt: 354.3361

ACTION – Immunomodulator and antiangiogenic agent, an analogue of the dipeptide L-Glu-L-Trp (also known as thymogen) in which the nitrogen in the indole group has been substituted with a carbon; it displays immunomodulating and antiangiogenic properties similar to those of the parent compound, while showing greater stability, better transport across the blood–brain barrier and mucous membranes, higher bioavailability and more resistance to enzymatic degradation. The compound is useful for the treatment of immunological disorders, infections, tissue damage and toxemia or anemia during pregnancy, and as a vaccine enhancer, as well as in the therapy of pathologies involving neovascularization.

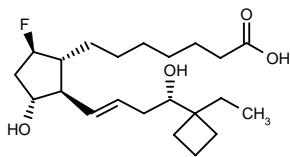
SOURCE – Cytran.

REFERENCES

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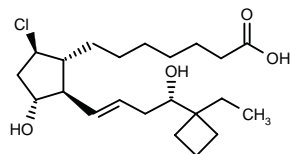
289643

9,15-Dideoxy-16(S)-(1-ethylcyclobutyl)-9-fluoro-16-hydroxy-17,18,19,20-tetranorprostaglandin F_{1β}

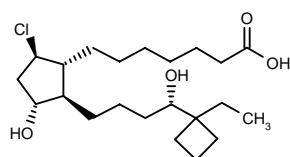


C22 H37 F O4; Mol wt: 384.5283

ACTION – Agent with potent and selective affinity for EP₂ receptors, as demonstrated in binding assays by K_i values of > 10, 0.066, > 10 and > 10 μM, respectively, for inhibition of [³H]-PGE₂ binding to murine EP₁, EP₂, EP_{3α} and EP₄ receptors cloned in CHO cells. The compound is expected to be useful in the treatment or prevention of immunological diseases such as autoimmune diseases or organ transplantation, asthma, abnormal bone formation, neuronal cell death, hepatic disorders, abortion or premature labor and glaucoma. Other compounds from this series of ω-cycloalkyl-prostaglandin E₁ derivatives are:



289644: C22 H37 Cl O4



289645: C22 H39 Cl O4

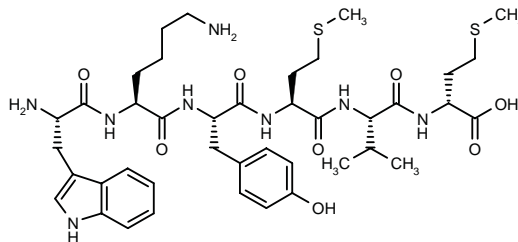
SOURCE – Ono.

REFERENCES

1. Ohuchida, S. and Tani, K. (Ono Pharmaceutical Co., Ltd.) *ω-Cycloalkyl-prostaglandin E₁ derivs., their preparation method, and medicinal compsns. containing them as active ingredient*. JP 2000095755.

289986

L-Tryptophyl-L-lysyl-L-tyrosyl-L-methionyl-L-valyl-D-methionine



C41 H60 N8 O8 S2; Mol wt: 857.1050

ACTION – Immunomodulating agent, a synthetic peptide proven to stimulate the bactericidal (*Staphylococcus aureus*) and candidicidal (*Candida albicans*) activities of monocytes derived from adult human peripheral blood and neonatal cord blood, with a maximal effect at 10 nM. In rats infected with *S. aureus*, treatment with the synthetic peptide (10 nmol/kg i.v.) rapidly reduced bacteria in blood compared to controls. Further experiments indicated that the peptide acts by increasing intracellular calcium levels and superoxide generation.

SOURCES – Pohang University of Science and Technology, Pohang (KR); Ulsan University, Seoul (KR).

REFERENCES

1. Ju, S.A. et al. *A novel peptide Trp-Lys-Tyr-Met-Val-D-Met, stimulates bactericidal and candidicidal activities of monocytes*. FASEB J 2000, 14(6): Abst 192.1.

C220

289093

Chimeric anti-human CD40 monoclonal antibody

ACTION – Immunosuppressant, a chimeric anti-human CD40 monoclonal antibody able to prolong renal allograft survival in rhesus monkeys from 9.5 days in controls to 54 days after treatment with a dose of 10 mg/kg i.v. on days 0, 2, 4, 7, 9, 11 and 14 following transplantation. Combination treatment with compound and human CTLA4-Ig did not improve survival rate but did inhibit the development of anti-donor antibodies, indicating synergistic immunosuppression.

SOURCE – Emory University, Atlanta, GA (US).

REFERENCES

1. Larsen, C.P. et al. *Prolongation of renal allograft survival by a chimeric anti-human CD40 monoclonal antibody in nonhuman primates*. Transplant 2000 (May 13-17, Chicago) 2000, Abst 45.

CLASP-1

288683

Cadherin-like asymmetry protein-1

ACTION – Mammalian cell-surface protein that is expressed in lymphoid tissues and the brain, in particular in both T- and B-cells, as well as macrophages; more importantly, it is concentrated at the interface between T-cell/B-cell clusters. The invention also includes polynucleotides encoding this protein, expression vectors containing these polynucleotides and antibodies that bind specifically to Clasp-1. The anti-Clasp-1 antibodies inhibit T-cell/B-cell interactions, thereby inhibiting the immune response, and may thus be useful in the treatment of autoimmune diseases and for the prevention of transplant rejection.

SOURCE – Leland Stanford Junior University, Palo Alto, CA (US).

REFERENCES

1. Lu, P.S. and Davis, M.M. (Leland Stanford Junior University) *Cadherin-like asymmetry protein-1, and methods for its use*. WO 0020434.

GONOCOCCAL Omp85

289703

Polypeptide from the outer membrane of Neisseria gonorrhoeae of about 792 amino acids and a predicted molecular weight of about 85,842 daltons

ACTION – Outer membrane protein of *Neisseria gonorrhoeae* suggested to play an important role in pathogen–host interactions. Polypeptides, fusion proteins or fragments thereof are useful for preparing vaccines for the therapy of diseases caused by this microorganism, especially for nonsymptomatic infections. A similar Omp85 outer membrane protein was isolated from *Neisseria meningitidis*.

Polypeptide from the outer membrane of Neisseria meningitidis of about 797 amino acids and a predicted molecular weight of about 88,500 daltons

Meningococcal Omp85 [289704]

SOURCE – University of Montana, Missoula, MT (US).

REFERENCES

1. Judd, R.C. and Manning, S.D. (University of Montana) *Omp85 proteins of Neisseria gonorrhoeae and Neisseria meningitidis, compsns. containing same and methods of use thereof*. WO 0023595.

JJ319

287646

Anti-CD28 monoclonal antibody

ACTION – Anti-CD28 monoclonal antibody proven highly effective in a rat model of chronic renal allograft rejection; a single dose of 0.5 mg i.v. on day 0 was associated with indefinite survival (> 120 days), as well as preservation of morphology and liver function. It is suggested to act by signaling T-cells to increase IL-2 production, rendering them more susceptible to activation-induced cell death, or by blocking the CD28 receptor, leading to an unopposed CTLA4-B7 interaction and T-cell anergy.

SOURCES – Akademia Medyczna w Warszawie, Warsaw (PL); Brigham & Women’s Hospital, Boston, MA (US); Harvard Medical School, Boston, MA (US).

REFERENCES

1. Laskowski, I.A. et al. *Signaling CD28 antibody prolongs survival and preserves renal allograft structure and function in a rat model of chronic rejection*. Transplant 2000 (May 13-17, Chicago) 2000, Abst 1169.

OX-40–MAYTANSINE

289088

Immunotoxin consisting of the OX-40 antigen conjugated to maytansine

ACTION – Immunotoxin expected to eliminate only T-helper cells responsive to graft alloantigens when given posttransplant, a monoclonal antibody against the T-cell surface marker CD134 conjugated to maytansine, a toxin directed against microtubule assembly. The conjugate completely inhibited the mixed lymphocyte response at 10 nM and gave an IC₅₀ of 4 nM.

SOURCES – Oregon Health Sciences University, Portland, OR (US); Veterans Affairs Medical Center, Portland, OR (US).

REFERENCES

1. Wagner, C.R. et al. *Targeted immunosuppression of alloreactivity with OX-40 immunotoxins*. Transplant 2000 (May 13-17, Chicago) 2000, Abst 324.

RTS,S/SBAS2^{1-7,9,12,15,18,20}

282997

Pre-erythrocytic recombinant malaria vaccine containing a portion of the circumsporozoite surface protein (CSP) of Plasmodium falciparum genetically linked to hepatitis B surface antigen (HBsAg), formulated with the adjuvant SBAS2

ACTION – Recombinant pre-erythrocytic malaria vaccine consisting of the circumsporozoite surface protein (CSP) of *Plasmodium falciparum* genetically linked to the hepatitis B surface antigen (HBsAg) incorporated with adjuvants to enhance humoral and cell-mediated immune responses (SBAS2 adjuvant system). The vaccine induced protection against *P. falciparum* sporozoite challenge in healthy volunteers; an RTS,S-specific lymphoproliferative response and antibodies to CSP were strongly induced in all volunteers, indicating that the vaccine is a potent inducer of Th1-type cellular and humoral immunity. A phase IIb clinical trial designed to evaluate the efficacy of vaccine in 306 semi-immune volunteers on a 0-, 1- and 5-month vaccination schedule showed marked increases in T-cell proliferation and cultured interferon gamma enzyme-linked immunospot (ELISPOT), indicating a strong immune response.

SOURCE – SmithKline Beecham.

REFERENCES

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- Cohen, J. *Malaria vaccine development: Approaches and status*. Clin Microbiol Infect 2000, 6(Suppl. 1): Abst TuS3.
- Doherty, J.F. et al. *A phase I safety and immunogenicity trial with the candidate malaria vaccine RTS,S/SBAS2 in semi-immune adults in The Gambia*. Am J Trop Med Hyg 1999, 61(6): 865.
- Gordon, D.M. et al. *Safety, immunogenicity, and efficacy of a recombinantly produced Plasmodium falciparum circumsporozoite protein-hepatitis B surface antigen subunit vaccine*. J Infect Dis 1995, 171(6): 1576.
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- Lalvani, A. et al. *Potent induction of focused Th1-type cellular and humoral immune responses by RTS,S/SBAS2, a recombinant Plasmodium falciparum malaria vaccine*. J Infect Dis 1999, 180(5): 1656.
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- Richards, R.L. et al. *Liposomes containing lipid A serve as an adjuvant for induction of antibody and cytotoxic T-cell responses against RTS,S malaria antigen*. Infect Immun 1998, 66(6): 2859.
- Schwenk, R. et al. *CS protein-specific opsonizing antibodies induced by the RTS,S malaria vaccine mediate protection*. Am J Trop Med Hyg 1999, 61(3, Suppl.): Abst 802.

14. Stoute, J.A. et al. *A preliminary evaluation of a recombinant circumsporozoite protein vaccine against Plasmodium falciparum malaria*. RTS,S Malaria Vaccine Evaluation Group. New Engl J Med 1997, 336(2): 86.

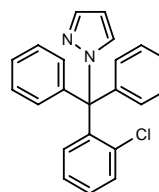
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16. SmithKline Beecham reaffirms commitment to preventing, treating diseases in the developing world. DailyDrugNews.com (Daily Essentials) 2000, March 9.

TRAM-34

290056

1-[(2-Chlorophenyl)(diphenyl)methyl]-1H-pyrazole



C22 H17 Cl N2; Mol wt: 344.8433

ACTION – Potent inhibitor of intermediate-conductance calcium-activated K⁺ (IK_{Ca}) channels (K_d = 20-25 nM) related to clotrimazole, with 200-1,500-fold selectivity versus other channels. Compound suppressed mitogen-stimulated [³H]-thymidine incorporation by human lymphocytes, but unlike clotrimazole, it did not exhibit inhibitory activity on cytochrome P-450-dependent enzymes. No acute toxicity was seen in mice after administration of compound at a dose 0.5 mg/kg i.v. Potentially useful for the treatment of autoimmune disorders, sickle cell disease and diarrhea.

SOURCE – University of California, Irvine, Irvine, CA (US).

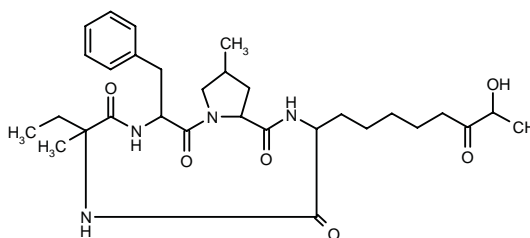
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- Wulff, H. et al. *TRAM-34, a novel inhibitor of the IK_{Ca} channel for immunosuppression, sickle cell disease and diarrhea*. FASEB J 2000, 14(8): Abst 289.

WF-27082B

288940

6-Ethyl-3-(7-hydroxy-6-oxooctyl)-6,13-dimethyl-9-benzylperhydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecine-1,4,7,10-tetraone



C30 H44 N4 O6; Mol wt: 556.6996

ACTION – Histone deacetylase inhibitor, a representative compound from a series of cyclic tetrapeptides isolated from a strain of *Acremonium* sp., potentially useful for the treatment or prevention of inflammatory disorders, diabetes and associated complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukemia (APL), protozoal infections, transplant rejection, autoimmune diseases and cancer. *In vitro*, compound concentration-dependently inhibited partially purified human histone deacetylase (37.3-98.6% inhibition at 10-1000 ng/ml), as well as anti-CD3 antibody-induced murine lymphocyte blastogenesis (46.1-114.1% inhibition at 3.1-25 ng/ml), and it exhibited IC₅₀ values of 11 and 14 ng/ml against human Jurkat T-cell leukemia and human colon adenocarcinoma HT-29 cells, respectively. *In vivo*, it was shown to inhibit the delayed-type hypersensitivity (DTH) response in mice, giving 47% inhibition at 100 mg/kg/day p.o. x 8 days.

SOURCE – Fujisawa.

REFERENCES

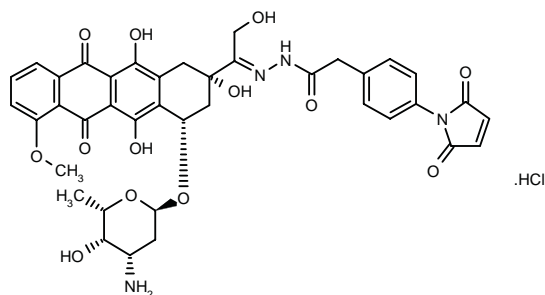
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ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

287489

N' -[1-[4(*S*)-(3-Amino-2,3,6-trideoxy- α -L-*lyxo*-hexopyranosyloxy)-2(*S*),5,12-trihydroxy-7-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydronaphthacen-2-yl]-2-hydroxyethylidene]-2-[4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-phenyl]acetohydrazide hydrochloride



C39 H38 N4 O13 . HCl; Mol wt: 807.2051

ACTION – Antineoplastic agent, a doxorubicin derivative whose thiol-binding group binds preferentially to endogenous serum albumin following incubation with human blood plasma or i.v. injection into mice. According to this macromolecular prodrug approach, active drug is released from the drug-albumin conjugate at the low pH values typical of lysosomes and endosomes of tumor cells. It was able to induce complete remission of primary kidney tumors in a murine renal carcinoma model and to prevent the formation of metastases in the lung; in this model, it showed superior antitumor effect compared to

optimal doses of doxorubicin. Such an approach may also be useful for overcoming the toxicity of chemotherapeutic agents, as well as drug resistance.

SOURCE – Universität Freiburg, Freiburg (DE).

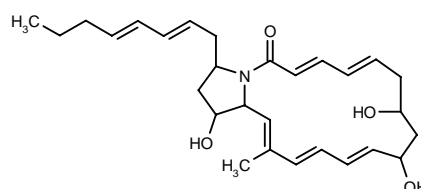
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2. Kratz, F. et al. *Preparation, characterization and in vitro efficacy of albumin conjugates of doxorubicin*. Biol Pharm Bull 1998, 21(1): 56.

BE-67251

289251

1,11,13-Trihydroxy-18-methyl-3-[(2*E*,4*E*)-octa-2,4-dienyl]-2,3,5,10,11,12,13,19a-octahydro-1*H*-pyrrolo[1,2-*a*]azacycloheptadecin-5-one



C28 H39 N O4; Mol wt: 453.6191

ACTION – Antitumor antibiotic isolated from *Streptomyces* sp. A67251 (FERM P-16789), shown to have antitumor activity against murine leukemia P388 cells (IC₅₀ = 7.7 μg/ml).

SOURCE – Banyu.

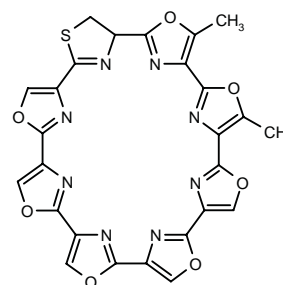
REFERENCES

1. Shimokawa, H. et al. (Banyu Pharmaceutical Co., Ltd.) *Antitumor substance BE-67251 and its preparation method*. JP 2000086664.

GM-95

289490

4,8-Dimethyl-3,7,11,15,19,23,27-hepta-oxa-31-thia-33,34,35,36,37,38,39,40-octaazanonacyclo[28.2.1.1^{2,5}.1^{6,9}.1^{10,13}.1^{14,17}.1^{18,21}.1^{22,25}.1^{26,29}]tetraconta-2(40),4,6(39),8,10(38),12,14(37),16,18(36),20,22(35),24,26(34),28,30(33)-pentadecaene



C26 H14 N8 O7 S; Mol wt: 582.5116

ACTION – Histone deacetylase inhibitor, a representative compound from a series of cyclic tetrapeptides isolated from a strain of *Acremonium* sp., potentially useful for the treatment or prevention of inflammatory disorders, diabetes and associated complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukemia (APL), protozoal infections, transplant rejection, autoimmune diseases and cancer. *In vitro*, compound concentration-dependently inhibited partially purified human histone deacetylase (37.3-98.6% inhibition at 10-1000 ng/ml), as well as anti-CD3 antibody-induced murine lymphocyte blastogenesis (46.1-114.1% inhibition at 3.1-25 ng/ml), and it exhibited IC₅₀ values of 11 and 14 ng/ml against human Jurkat T-cell leukemia and human colon adenocarcinoma HT-29 cells, respectively. *In vivo*, it was shown to inhibit the delayed-type hypersensitivity (DTH) response in mice, giving 47% inhibition at 100 mg/kg/day p.o. x 8 days.

SOURCE – Fujisawa.

REFERENCES

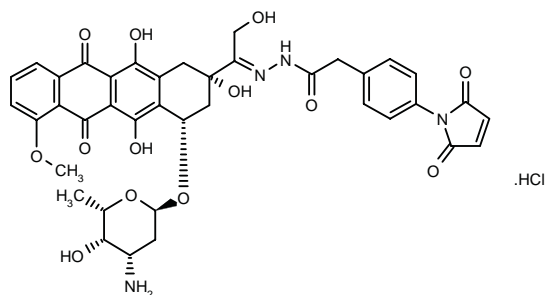
1. Mori, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Cyclic tetrapeptide cpd. and use thereof*. WO 0021979.

ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

287489

N' -[1-[4(*S*)-(3-Amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyloxy)-2(*S*),5,12-trihydroxy-7-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydronaphthacen-2-yl]-2-hydroxyethylidene]-2-[4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-phenyl]acetohydrazide hydrochloride



C39 H38 N4 O13 . HCl; Mol wt: 807.2051

ACTION – Antineoplastic agent, a doxorubicin derivative whose thiol-binding group binds preferentially to endogenous serum albumin following incubation with human blood plasma or i.v. injection into mice. According to this macromolecular prodrug approach, active drug is released from the drug-albumin conjugate at the low pH values typical of lysosomes and endosomes of tumor cells. It was able to induce complete remission of primary kidney tumors in a murine renal carcinoma model and to prevent the formation of metastases in the lung; in this model, it showed superior antitumor effect compared to

optimal doses of doxorubicin. Such an approach may also be useful for overcoming the toxicity of chemotherapeutic agents, as well as drug resistance.

SOURCE – Universität Freiburg, Freiburg (DE).

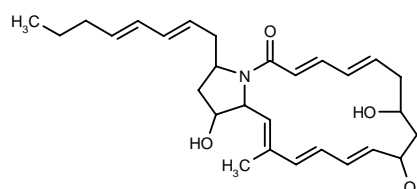
REFERENCES

1. Kratz, F. et al. *A novel macromolecular prodrug concept exploiting endogenous serum albumin as a drug carrier for cancer chemotherapy*. J Med Chem 2000, 43(7): 1253.
2. Kratz, F. et al. *Preparation, characterization and in vitro efficacy of albumin conjugates of doxorubicin*. Biol Pharm Bull 1998, 21(1): 56.

BE-67251

289251

1,11,13-Trihydroxy-18-methyl-3-[(2*E*,4*E*)-octa-2,4-dienyl]-2,3,5,10,11,12,13,19a-octahydro-1*H*-pyrrolo[1,2-*a*]azacycloheptadecin-5-one



C28 H39 N O4; Mol wt: 453.6191

ACTION – Antitumor antibiotic isolated from *Streptomyces* sp. A67251 (FERM P-16789), shown to have antitumor activity against murine leukemia P388 cells (IC₅₀ = 7.7 μg/ml).

SOURCE – Banyu.

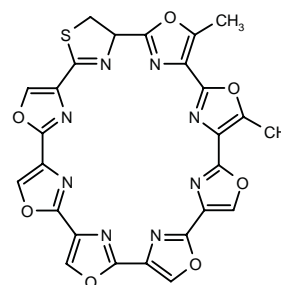
REFERENCES

1. Shimokawa, H. et al. (Banyu Pharmaceutical Co., Ltd.) *Antitumor substance BE-67251 and its preparation method*. JP 2000086664.

GM-95

289490

4,8-Dimethyl-3,7,11,15,19,23,27-hepta-oxa-31-thia-33,34,35,36,37,38,39,40-octaazanonacyclo[28.2.1.1^{2,5}.1^{6,9}.1^{10,13}.1^{14,17}.1^{18,21}.1^{22,25}.1^{26,29}]tetraconta-2(40),4,6(39),8,10(38),12,14(37),16,18(36),20,22(35),24,26(34),28,30(33)-pentadecaene



C26 H14 N8 O7 S; Mol wt: 582.5116

ACTION – Antineoplastic agent isolated from *Streptomyces anulatus* strain 3533-SV4 (FERM BP-6460) with telomerase-inhibitory activity ($IC_{50} = 50$ nM). Compound inhibited the proliferation of several human cancer cell lines such as ovarian cancer OVCAR-3, prostate cancer PC-3, breast cancer MCF-7, colon cancer KM12C-SM and pancreatic cancer PAN-3, and murine renal cancer Renca ($IC_{50} = 3.41, 8.82, 7.73, 3.74, 7.09$ and 0.97 μ M, respectively), being somewhat less active than 5-fluorouracil ($0.37, 5.7, 1.12, 1.32, 8.82$ and 0.58 μ M, respectively).

SOURCE – Taiho.

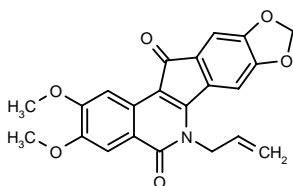
REFERENCES

1. Seto, H. et al. (Taiho Pharmaceutical Co., Ltd.) *Substance GM-95, process for producing the same and utilization thereof*. WO 0024747.

DNA-INTERCALATING DRUGS

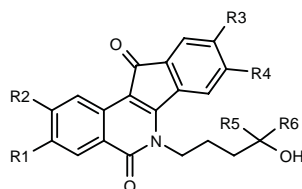
289045

6-Allyl-2,3-dimethoxy-6,12-dihydro-5*H*-[1,3]dioxolo-[5,6]indeno[1,2-*c*]isoquinoline-5,12-dione

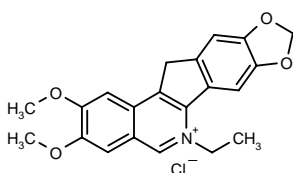


C22 H17 N O6; Mol wt: 391.3773

ACTION – Antineoplastic agent reported to act, at least in part, via inhibition of topoisomerase I. Compound exhibited GI_{50} values of 3.4, 2.3, 2.2, 6.6, 2.6, 3.2 and 5.2 μ M, respectively, against human lung HOP-62, colon HCT-116, CNS SF-539, ovarian OVCAR-3, renal SN12C, prostate DU-145 and breast MDA-MB-435 cancer cell lines, and is reported to inhibit topoisomerase I with activity 20-50% that of 1 μ M camptothecin. Other compounds from this series of indenoisoquinolines include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
289046	OMe	OMe	-OCH2O-	H	H	H	C ₂₃ H ₂₁ NO ₇
289047	H	H	H	H	-O-	H	C ₂₀ H ₁₅ NO ₄



289048: C21 H20 Cl N O4

SOURCES – Department of Health & Human Services (US); Purdue Research Foundation, West Lafayette, IN (US).

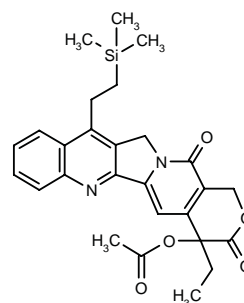
REFERENCES

1. Cushman, M.S. et al. (Purdue Research Foundation; Department of Health & Human Services) *Novel indenoisoquinolines as antineoplastic agents*. WO 0021537.

289082

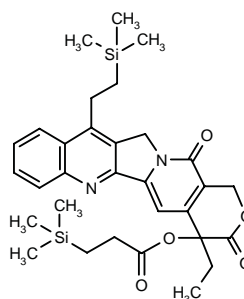
Acetic acid 4-ethyl-3,14-dioxo-11-[2-(trimethylsilyl)ethyl]-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]-quinolin-4-yl ester

20-*O*-Acetyl-7-[2-(trimethylsilyl)ethyl]camptothecin



C27 H30 N2 O5 Si; Mol wt: 490.6290

ACTION – Antitumor camptothecin derivative, a potent inhibitor of topoisomerase I with enhanced tissue penetration due to its lipophilic nature and greater lactone form stability in alkaline pH environments. Since the lactone form is correlated with antitumor activity and the open form is associated with unwanted toxicity, compound has a good profile as an antineoplastic agent. Another exemplified camptothecin derivative is:



289084: C31 H40 N2 O5 Si2

SOURCE – BioNumerik.

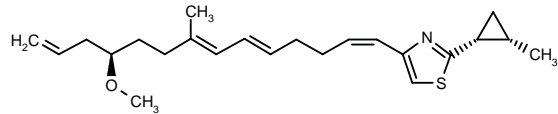
REFERENCES

1. Haridas, K. and Hausheer, F.H. (BioNumerik Pharmaceuticals, Inc.) *Highly lipophilic camptothecin derivs*. US 6057303.

ANTIMITOTIC DRUGS

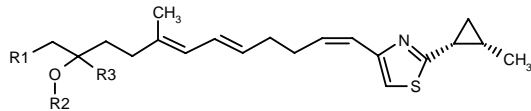
288949

4-[11(R)-Methoxy-8-methyl-1(Z),5(E),7(E),13-tetra-decatetraenyl]-2-[(1R,2S)-2-methylcyclopropyl]thiazole

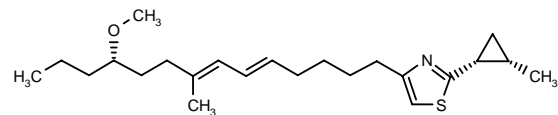


C23 H33 N O S; Mol wt: 371.5857

ACTION – Antineoplastic agent, a curacin A analogue that acts as an antimitotic agent, interfering with cellular mechanisms of tubulin formation, and is also expected to exhibit herbicidal activity. In addition, compound is reported to possess improved chemical stability compared to curacin A, which is believed to be due to the presence of a thiazole ring instead of the thiazoline ring of curacin A. Compound displayed potent antimitotic activity in the NCI 60 human tumor cell line panel. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Isomer	Formula
288952	Et	Me	H	S	C ₂₃ H ₃₅ NOS
288954	vinyl	Me	H	R	C ₂₃ H ₃₃ NOS
288956	vinyl	Me	H	R	C ₂₃ H ₃₃ NOS
288958	vinyl	H	H	R	C ₂₂ H ₃₁ NOS
288961	vinyl	-CH ₂ CH ₂ O-			C ₂₄ H ₃₃ NO ₂ S



288951: C23 H37 N O S

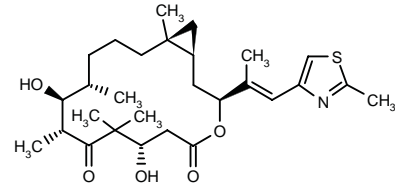
SOURCE – Oregon State University, Corvallis, OR (US).

REFERENCES

1. Gerwick, W.H. et al. (Oregon State University) *Curacin A analogs exhibiting antiproliferative activity against cells*. US 6057348.

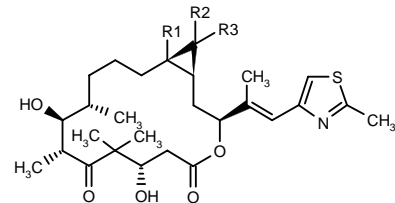
289575

(1S,3S,7S,10R,11S,12S,16S)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2(E)-(2-methylthiazol-4-yl)vinyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione



C28 H43 N O5 S; Mol wt: 505.7157

ACTION – Antineoplastic agent, an inhibitor of tubulin polymerization ($EC_{0.01} = 2.1 \mu M$) with cytotoxic activity against human colon carcinoma HCT 116 cells ($IC_{50} = 0.7 nM$); compound was about 2-3-fold more active than paclitaxel against tubulin polymerization and HCT 116 cells ($EC_{0.01} = 4.6$ and $IC_{50} = 2.3 nM$, respectively). Other epothilone cyclopropane analogues include the following:



Compound	R1	R2	R3	Formula
289576	H	H	H	C ₂₇ H ₄₁ NO ₅ S
289577	Me	Cl	Cl	C ₂₈ H ₄₁ Cl ₂ NO ₅ S
289578	Me	Br	Br	C ₂₈ H ₄₁ Br ₂ NO ₅ S

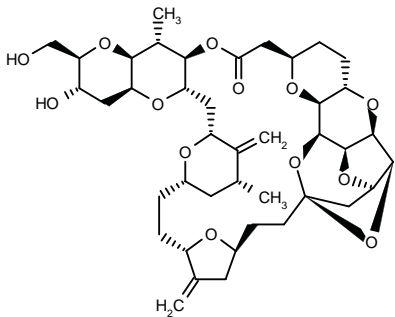
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Kim, S.-H.K. et al. (Bristol-Myers Squibb Co.) *12,13-Modified epothilone derivs*. WO 9954318, WO 9954319.
2. Johnson, J. et al. *Synthesis, structure proof, and biological activity of epothilone cyclopropanes*. Org Lett 2000, 2(11): 1537.

289873

(1R,2R,3aR,3bS,5R,8S,11S,14S,16R,18R,19aS,20aS,22S,23R,24aS,25S,25aR,29R,30aS,31S,32aR)-22-Hydroxy-23-(hydroxymethyl)-16,25-dimethyl-10,15-dimethylideneperhydro-1,5:8,11,14,18-triepoxy-29,31-ethano-2,5-methanofuro[2',3':5,6]pyrano[4,3-b]pyrano[2',3':5,6]pyrano[3,2-*l*][1,4,8]trioxacyclopentacosin-27-one



C41 H58 O13; Mol wt: 758.8962

ACTION – Antineoplastic agent, an analogue of halichondrin B, a polyether macrolide isolated from several marine sponges. Compound exhibited improved cytotoxic activity compared to paclitaxel against selected cancer cell lines including human colon cancer DLD-1, human histiocytic lymphoma U937, multidrug-resistant murine leukemia P388/VMDRC0.4 and parental murine leukemia P388 cells (IC₅₀ = 3.4, 220, 8.2 and 0.71 nM, respectively, vs. 27, 230, 16 and 170 nM, respectively). It inhibited both tubulin polymerization and microtubule assembly and induced cell cycle arrest, maintaining mitotic block 10 h after drug washout, probably due to tight binding to its macromolecular target or to efficient retention within the cell.

SOURCE – Eisai.

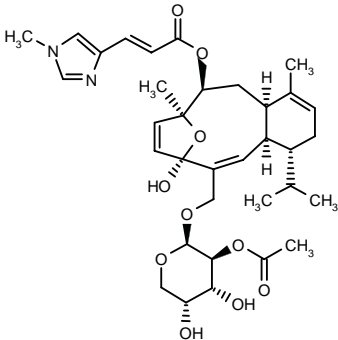
REFERENCES

1. Wang, Y. et al. *Structure-activity relationships of halichondrin B analogues: Modifications at C.30-C.38.* Bioorg Med Chem Lett 2000, 10(10): 1029.

DESMETHYLELEUTHEROBIN

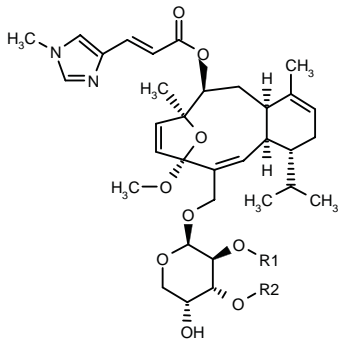
289539

3-(1-Methylimidazol-4-yl)-2(*E*)-propenoic acid (1*R*,4*aR*,6*S*,7*S*,10*R*,12*aR*)-11-(2-*O*-acetyl-β-D-arabinopyranosyloxymethyl)-4,7-dimethyl-10-hydroxy-1-isopropyl-1,2,4*a*,5,6,7,10,12*a*-octahydro-7,10-epoxybenzocyclo-dodecen-6-yl ester

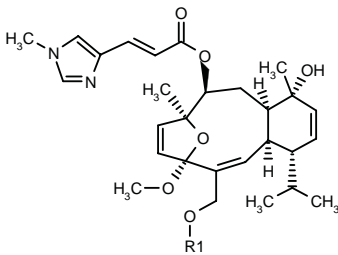


C34 H46 N2 O10; Mol wt: 642.7414

ACTION – Antimitotic agent, a diterpenoid analogue of eleutherobin extracted from the Caribbean octocoral *Erythropodium caribaeorum*. Compound exhibited antimitotic activity in a cell-based assay, with an IC₅₀ of 20 nM; IC₅₀ = 100 nM for eleutherobin. Other compounds isolated from this source are:



Compound	R1	R2	Isomer	Formula
Desacetyteleutherobin [289545]	H	H	E	C ₃₃ H ₄₆ N ₂ O ₉
Isoeleutherobin A [289546]	H	Ac	E	C ₃₅ H ₄₈ N ₂ O ₁₀
Z-Eleutherobin [289547]	Ac	H	Z	C ₃₅ H ₄₈ N ₂ O ₁₀



Compound	R1	Formula
Caribaeoside [289548]	2- <i>O</i> -Ac-β-D-arabinopyranosyl	C ₃₅ H ₄₈ N ₂ O ₁₁
Carbaeolin [289551]	Ac	C ₃₀ H ₄₀ N ₂ O ₇

SOURCE – University of British Columbia, Vancouver, BC (CA).

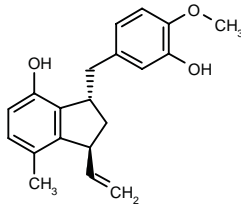
REFERENCES

1. Cinel, B. et al. *Antimitotic diterpenes from Erythropodium caribaeorum test pharmacophore models for microtubule stabilization.* Org Lett 2000, 2(3): 257.

RPR-115781

289441

3(*S*)-(3-Hydroxy-4-methoxybenzyl)-7-methyl-1(*S*)-vinyl-2,3-dihydro-1*H*-inden-4-ol



C20 H22 O3; Mol wt: 310.3908

ACTION – Microtubule assembly inhibitor extracted from the Indian plant *Ottelia alismoides*, proven to reversibly bind to tubulin and inhibit microtubule assembly with an IC₅₀ of 6 μM. Compound exhibited *in vitro* cytotoxic activity and was seen to arrest cells in the G2/M phase of the cell cycle. Considered a lead compound for further chemical modification in order to find more active substances with potential therapeutic utility as anticancer agents.

SOURCE – Aventis Pharma.

REFERENCES

1. Combeau, C. et al. *RPR112378 and RPR115781: Two representatives of a new family of microtubule assembly inhibitors.* Mol Pharmacol 2000, 57(3): 553.

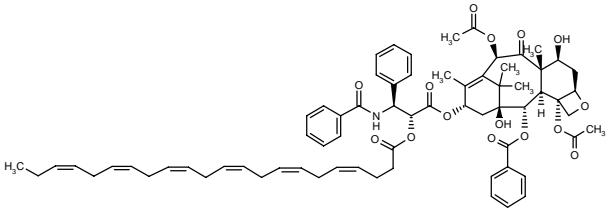
TAXOPREXIN™

277994

2'-(*all-cis*-Docosahexaenoyl)paclitaxel

[2*aR*-[2*a*α,4β,4*a*β,6β,9α(2*R*,3*S*),11β,12α,12*a*α,12*b*α]-6,12*b*-Diacetoxy-9[3-benzamido-2-[4(*Z*),7(*Z*),10(*Z*),13(*Z*),16(*Z*),19(*Z*)-docosahexaenoyl]-3-phenylpropionyloxy]-12-(benzoyloxy)-4,11-dihydroxy-4*a*,8,13,13-tetramethyl-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one

DHA-paclitaxel



C69 H81 N O15; Mol wt: 1164.3910

ACTION – Antineoplastic agent, a novel taxane made by chemically linking the active compound paclitaxel and the fatty acid docosahexaenoic acid (DHA), which improves the pharmacological disposition of paclitaxel. The conjugate demonstrated potent antitumor activity, greater than that of paclitaxel, in a number of preclinical tumor models and was less toxic than paclitaxel in mice, rats and dogs; the volume of distribution and plasma clearance were 74- and 94-fold lower, respectively, than those of paclitaxel. Studies on the distribution of the conjugate in patients demonstrated that it is not significantly degraded to paclitaxel in the blood (< 1/1000 of conjugate is released as free paclitaxel) and that it has a long half-life of 2 days, which is 4 times longer than that of paclitaxel.

SOURCE – Neuromedica.

REFERENCES

1. Bradley, M.G. et al. (Neuromedica, Inc.) *Conjugates of cis-docosahexaenoic acid and paclitaxel*. US 5919815, WO 9744336.

2. Bradley, M.G. et al. (Neuromedica, Inc.) *DHA-pharmaceutical agent conjugates*. US 5795909, WO 9744063.

3. Bradley, M.O. et al. *Increased therapeutic index by conjugation of a natural fatty acid to paclitaxel*. Proc Amer Assoc Cancer Res 2000, 41: Abst 1929.

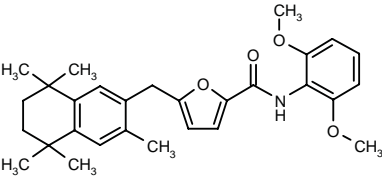
4. Wolff, A.C. et al. *Phase I study of taxoprexin DHA-paclitaxel (TXP), a novel taxane with unique preclinical activity, pharmacology, and toxicity profile*. Proc Am Soc Clin Oncol 2000, 19: Abst 921E.

5. *Company Profile: Neuromedica*. DailyDrugNews.com (Daily Essentials) 1999, June 23.

HORMONAL AGENTS

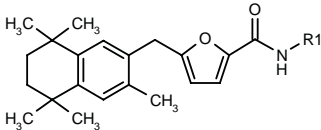
288639

N-(2,6-Dimethoxyphenyl)-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-ylmethyl)furan-2-carboxamide



C29 H35 N O4; Mol wt: 461.5985

ACTION – Nonpeptide gonadotropin-releasing hormone (GnRH) antagonist with potential for the treatment of steroid-dependent tumors and reproductive disorders, as well as for regulating fertility. *In vitro*, compound exhibited potent affinity for human GnRH receptors expressed in HEK293 cells (IC₅₀ = 8.0 ± 0.9 nM) and high selectivity relative to a wide range of other receptors tested. *In vivo*, compound produced a maximal suppression of luteinizing hormone (LH) levels of 78 and 59% at 10 mg/kg i.v. and 50 mg/kg p.o., respectively, in castrated rats. Other specifically claimed compounds include the following:



Compound	R1	Formula
288641	4-[NH2C(=NH)NHCH2]-cyclohexyl-CH2	C ₃₀ H ₄₄ N ₄ O ₂
288643	trans-4-[NH2C(=NH)NHCH2]-cyclohexyl-CH2	C ₃₀ H ₄₄ N ₄ O ₂
288645	3-[4-(2-THF-CH2NH)-2-pyrimidinyl-NHCH2]-cyclohexyl-CH2	C ₃₈ H ₅₃ N ₅ O ₃
288646	trans-4-CO2H-cyclohexyl-CH2	C ₂₉ H ₃₉ NO ₄
288647	5-Me-2-pyrazinyl-CH2	C ₂₇ H ₃₃ N ₃ O ₂
288649	4-Me-PhCH2	C ₂₉ H ₃₅ NO ₂
288650	2,3-(MeO)2-PhCH2	C ₃₀ H ₃₇ NO ₄
288652	4-CN-cyclohexyl-CH2	C ₂₉ H ₃₈ N ₂ O ₂
288653	2,3-(Me)2-PhCH2	C ₃₀ H ₃₇ NO ₂
288655	3,4-(Me)2-PhCH2	C ₃₀ H ₃₇ NO ₂
288656	3-Ac-Ph	C ₂₉ H ₃₃ NO ₃

SOURCE – Agouron (Pfizer).

REFERENCES

1. Anderson, M.B. et al. (Agouron Pharmaceuticals, Inc.) *Non-peptide GnRH agent, methods and intermediates for their preparation*. WO 0020358.

CANCER IMMUNOTHERAPY

GELDANAMYCIN-HERCEPTIN™ IMMUNOCONJUGATE

290004

Immunoconjugate consisting of 17-[3-[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)butanamido]propylamino]geldanamycin, 17-GMB-ABA-GA, conjugated to the anti-HER2 monoclonal antibody Herceptin™

ACTION – Antineoplastic agent, an immunoconjugate comprising the anti-HER2 monoclonal antibody Herceptin™ (trastuzumab) bound through a bifunctional crosslinker to the highly cytotoxic drug geldanamycin. The immunoconjugate exhibited anti-proliferative activity against MDA-361/DYT2, an HER2-positive human breast cancer cell line (IC₅₀ = 0.5 mg/ml), producing an approximately 4-fold greater reduction in growth as compared with Herceptin™ alone. Other experiments are ongoing to evaluate the *in vivo* efficacy of this conjugate in animal xenograft models.

SOURCE – National Cancer Institute, Bethesda, MD (US).

REFERENCES

1. Mandler, R. et al. *Synthesis and evaluation of antiproliferative activity of geldanamycin-Herceptin™ immunoconjugate*. Bioorg Med Chem Lett 2000, 10(10): 1025.

Hu1D10

229801

Humanized chimeric antibody directed against an HLA-DR β -chain epitope variably expressed on lymphocytes, macrophages and dendritic cells along with malignant B-lymphocytes

NSC-704867
SMART 1D10 antibody

ACTION – Humanized monoclonal antibody directed against an HLA-DR β -chain epitope variably expressed on lymphocytes, macrophages and dendritic cells along with malignant B-lymphocytes. Compound was seen to induce apoptosis in human chronic lymphocytic leukemia cell lines and fresh human B-cell tumors independent of complement-mediated lysis and of anti-Fc γ -specific crosslinking. Nonhuman primate studies demonstrated that repeated infusions of compound are safe under controlled conditions and result in B-cell depletion. A phase I dose-escalation study in patients with relapsed 1D10+ B-cell lymphomas indicated that compound (0.15-1.5 mg/kg infused for 2 h 4 times/week) was well tolerated, with no significant metabolic, hepatic, neurological or hematological toxicity; some evidence of tumor response was seen. Potentially useful for the treatment of non-Hodgkin's lymphoma.

SOURCES – University of Iowa, Iowa City, IA (US); National Cancer Institute, Bethesda, MD (US); Protein Design Labs.

REFERENCES

1. Byrd, J.C. et al. *Hu1D10 induces apoptosis in vitro in human chronic lymphocytic leukemia cells (CLL) independent of complement mediated lysis but requires Fc γ receptor ligation*. 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 1405.
2. Klingbeil, C. and Hsu, D.H. *Pharmacology and safety assessment of humanized monoclonal antibodies for therapeutic use*. Toxicol Pathol 1999, 27(1): 1.
3. Link, B.K. et al. *Phase I trial of humanized 1D10 (Hu1D10) monoclonal antibody targeting class II molecules in patients with relapsed lymphoma*. Proc Am Soc Clin Oncol 2000, 19: Abst 86.
4. *National Cancer Institute study concludes PDL bispecific antibody is effective in animal model of solid tumors*. Protein Design Labs, Inc. Press Release 1995, Aug 16.
5. *Phase I trial begins for SMART 1D10 antibody in non-Hodgkin's B-cell lymphoma*. DailyDrugNews.com (Daily Essentials) 1999, Aug 5.
6. *Protein Design Labs updates R&D efforts for Q4 and full year 1999*. DailyDrugNews.com (Daily Essentials) 2000, Jan 10.
7. *Protein Design Labs, Inc.. Oppenheimer & Co., Inc. Equity Report 1995, June 8*.

IRX-2

289132

Mixture of cytokines obtained from unrelated donor lymphocytes that have been used to induce immune regression of tumors

ACTION – Natural cytokine mixture proven to induce immune-mediated tumor regression. Phase II clinical studies in patients with stage II-IV squamous cell cancer of the head and neck or early-stage cervical carcinoma demonstrated that peritumoral infiltration with the mixture, in combination with low-dose infusion of cyclophosphamide, oral indomethacin and zinc in a 21-day cycle prior to surgery or radiotherapy, induces lymphocyte mobilization and clinical and histological changes indicative of immune-mediated tumor regression. The mixture exhibited minimal toxicity and improved overall survival, and is considered a candidate for phase III clinical trials.

SOURCE – Instituto Nacional de Cancerología, Mexico, D.F. (MX).

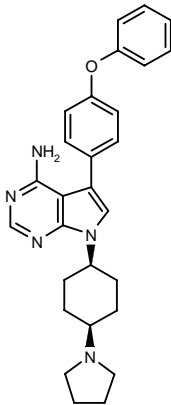
REFERENCES

1. Barrera, J.L. et al. *Combination immunotherapy of squamous cell carcinoma of the head and neck: A phase 2 trial*. Arch Otolaryngol - Head Neck Surg 2000, 126(3): 345.
2. Dueñas, A. et al. *Neoadjuvant treatment with a natural cytokine mixture (IRX2) in early stage cervical carcinoma*. 10th Int Congr Anti-Cancer Treat (Jan 31-Feb 3, Paris) 2000, Abst P071.
3. Meneses, A. et al. *Histologic findings in patients with head and neck squamous cell carcinoma receiving perilymphatic natural cytokine mixture (IRX-2) prior to surgery*. Arch Pathol Lab Med 1998, 122(5): 447.
4. Verasategui, E. et al. *A natural cytokine mixture (IRX-2) and interference with immune suppression induce immune mobilization and regression of head and neck cancer*. Int J Immunopharmacol 1997, 19(11-12): 619.

INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

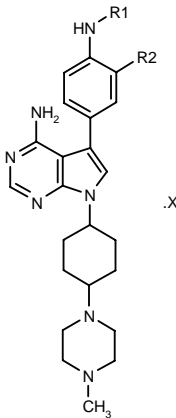
287830

cis-5-(4-Phenoxyphenyl)-7-[4-(pyrrolidin-1-yl)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylamine

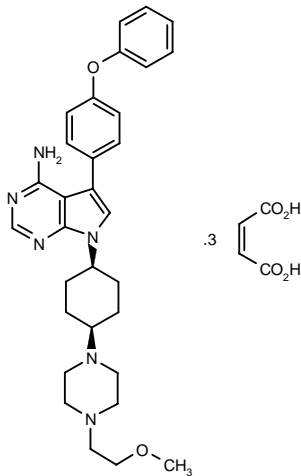


C28 H31 N5 O; Mol wt: 453.5869

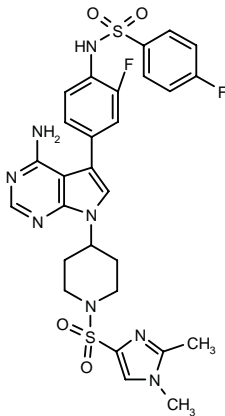
ACTION – An inhibitor of serine/threonine and tyrosine kinases involved in angiogenic, hyperproliferative or immunological processes, a representative compound from a series of pyrrolopyrimidine derivatives, wherein the following are also included:



Compound	R1	R2	Isomer	X	Formula
287833	COCH2CH2Ph	OMe	trans		C ₃₃ H ₄₁ N ₇ O ₂
287835	3-F-PhSO2	F	cis	dimaleate	C ₂₉ H ₃₃ F ₂ N ₇ O ₂ S .2C ₄ H ₄ O ₄
287836	2,1,3-benzothia- diazol-4-yl-SO2	F	cis	trimaleate	C ₂₉ H ₃₂ FN ₉ O ₃ S .3C ₄ H ₄ O ₄
287837	3,4-(F)2-PhSO2	F	trans	trimaleate	C ₂₉ H ₃₂ F ₃ N ₇ O ₂ S .3C ₄ H ₄ O ₄
287838	5-Me-2,1,3-benzo- thiadiazol-4-yl-SO2	F	trans	trimaleate	C ₃₀ H ₃₄ FN ₉ O ₂ S ₂ .3C ₄ H ₄ O ₄



287832: C31 H38 N6 O2 . 3 C4 H4 O4



287834: C28 H28 F2 N8 O4 S2

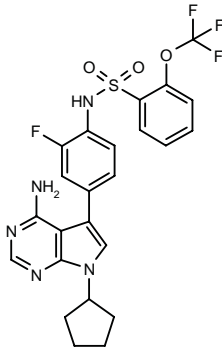
SOURCE – BASF.

REFERENCES

1. Hirst, G.C. et al. (BASF AG) *Pyrrolopyrimidines as protein kinase inhibitors*. WO 0017203.

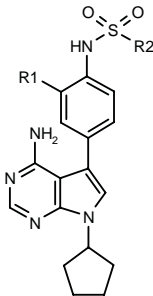
287877

N-[4-(4-Amino-7-cyclopentyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl]-2-(trifluoromethoxy)]benzene-sulfonamide



C24 H21 F4 N5 O3 S; Mol wt: 535.5199

ACTION – An inhibitor of serine/threonine and tyrosine kinases involved in angiogenic, hyperproliferative or immunological processes, a representative compound from a series of 4-aminopyrrolopyrimidine derivatives, wherein the following are also specifically claimed:



Compound	R1	R2	Formula
287878	Cl	Ph	C ₂₃ H ₂₂ ClN ₅ O ₂ S
287879	F	2-NO ₂ -Ph	C ₂₃ H ₂₁ FN ₅ O ₄ S
287880	F	4-Br-2-F-Ph	C ₂₃ H ₂₀ BrF ₂ N ₅ O ₂ S
287881	F	2-Cl-4-F-Ph	C ₂₃ H ₂₀ ClF ₂ N ₅ O ₂ S
287882	F	2-Cl-4-CN-Ph	C ₂₄ H ₂₀ ClFN ₆ O ₂ S
287883	F	3-Br-5-Cl-2-thienyl	C ₂₁ H ₁₈ BrClFN ₅ O ₂ S ₂
287884	F	5-Cl-2,1,3-benzothiadiazol-4-yl	C ₂₃ H ₁₉ ClFN ₇ O ₂ S ₂

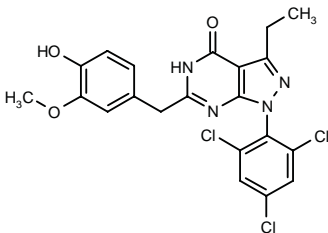
SOURCE – BASF.

REFERENCES

1. Calderwood, D. et al. (BASF AG) *4-Aminopyrrolopyrimidines as kinase inhibitors*. WO 0017202.

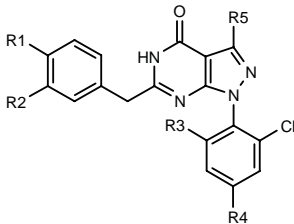
289023

3-Ethyl-6-(4-hydroxy-3-methoxybenzyl)-1-(2,4,6-trichloro-phenyl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one



C21 H17 Cl3 N4 O3; Mol wt: 479.7493

ACTION – Cyclin-dependent kinase inhibitor expected to be of use for the treatment of cancer and other proliferative diseases. A representative compound from a series of 6-substituted pyrazolo[3,4-*d*]pyrimidin-4-one derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
289024	OH	H	Me	H	Et	C ₂₁ H ₁₉ ClN ₄ O ₂
289025	H	NH2	Cl	Cl	i-Pr	C ₂₁ H ₁₈ Cl ₃ N ₅ O
289026	CH2CONH-CH2CH2N(Me)2	H	Cl	H	i-Pr	C ₂₇ H ₃₀ Cl ₂ N ₆ O ₂
289027	4-morpholinyl-CH2CONH	H	Cl	Cl	i-Pr	C ₂₇ H ₂₇ Cl ₃ N ₆ O ₃
289028	2-Piz-CONH	H	Cl	Cl	i-Pr	C ₂₆ H ₂₆ Cl ₃ N ₇ O ₂
289029	4-morpholinyl-CH2CH2NHCONH	H	Cl	Cl	i-Pr	C ₂₈ H ₃₀ Cl ₃ N ₇ O ₃
289030	NHCOCH2N(Me)2	H	Cl	Cl	cyclopropyl	C ₂₅ H ₂₃ Cl ₃ N ₆ O ₂
289031	H	OMe	Cl	SO2NH2	i-Pr	C ₂₂ H ₂₁ Cl ₂ N ₅ O ₄ S

SOURCE – DuPont Pharmaceuticals.

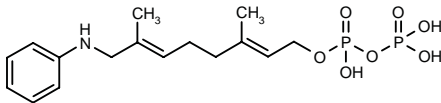
REFERENCES

1. Markwalder, J.A. et al. (DuPont Pharmaceuticals Co.) *6-Substd. pyrazolo[3,4-*d*]pyrimidin-4-ones useful as cyclin dependent kinase inhibitors*. WO 0021926.

289572

Diphosphoric acid mono[3,7-dimethyl-8-(phenylamino)-2(*E*),6(*E*)-octadienyl] ester

8-Anilinogeranyl pyrophosphate



C16 H25 N O7 P2; Mol wt: 405.3215

ACTION – Farnesyl pyrophosphate analogue proven to inhibit protein farnesyltransferase-catalyzed Ras farnesylation (K_i = 0.03 μ M; IC_{50} = 0.5 μ M), with lower activity against geranylgeranyltransferase-I (IC_{50} = 20 μ M) and inactive against squalene synthase (IC_{50} = 1000 μ M).

SOURCE – University of Kentucky, Lexington, KY (US).

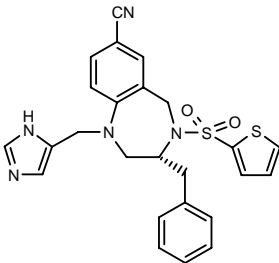
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1. Chehade, K.A. et al. *Design and synthesis of a transferable farnesyl pyrophosphate analogue to Ras by protein farnesyltransferase*. J Org Chem 2000, 65(10): 3027.

BMS-214662

287194

3(*R*)-Benzyl-1-(1*H*-imidazol-5-ylmethyl)-4-(2-thienylsulfonyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-7-carbonitrile



C25 H23 N5 O2 S2; Mol wt: 489.6217

ACTION – Antineoplastic agent, a potent and selective protein farnesyltransferase inhibitor shown to strongly inhibit both H-Ras and K-Ras farnesylation *in vitro*, although it is significantly more potent against H-Ras (IC₅₀ = 0.7 nM vs. 19 nM for K-Ras); it shows 1,000-fold selectivity over human geranylgeranyltransferase. Compound induced reversion to normal phenotype in H-Ras-transformed cancer cells, inhibited anchorage-independent growth of human tumor cell lines and potently induced apoptosis in human cancer cells. Antitumor activity was observed following both parenteral and oral administration in mice bearing human tumor xenografts including colon carcinoma HCT 116, colon adenocarcinoma HT-29, bladder cancer EJ-1, pancreatic carcinoma MIA PaCa-2 and lung carcinoma Calu-1 tumors, as well as a multidrug-resistant HCT 116 subline. Further studies with the compound in mice indicated that it exerts chemopreventive in addition to therapeutic antitumor activity. In phase I clinical studies, when given by intermittent i.v. infusions every 3 weeks at escalating doses of 36-225 mg/m² to patients with advanced solid tumors, it induced acute and transient elevations in transaminases and gastrointestinal toxicity at the highest dose, with no cumulative toxicity. Oral administration was also not associated with dose-limiting toxicity, adverse events mainly consisting of mild to moderate gastrointestinal toxicity.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Ding, C.Z. et al. (Bristol-Myers Squibb Co.) *Inhibitors of farnesyl protein transferase*. EP 0892797, JP 2000502356, US 6011029, WO 9730992.

2. Bol, D.K. et al. *A comparison of the therapeutic and preventive efficacy of a novel ras farnesyltransferase inhibitor in endogenous mouse carcinogenesis models*. Proc Amer Assoc Cancer Res 2000, 41: Abst 1400.

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4. Hunt, J.T. and Manne, V. *Farnesyltransferase inhibitors: From peptidomimetics to the clinical agent BMS-214662*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 294.

5. Manne, V. et al. *BMS-214662, a highly potent apoptotic farnesyltransferase inhibitor*. Proc Amer Assoc Cancer Res 2000, 41: Abst 1399.

6. Manne, V. et al. *BMS-214662, a nonthiol small molecule farnesyltransferase inhibitor*. Proc Amer Assoc Cancer Res 2000, 41: Abst 2835.

7. Rose, W.C. et al. *Preclinical antitumor activity of BMS-214662, a novel farnesyltransferase inhibitor (FTI)*. Proc Amer Assoc Cancer Res 2000, 41: Abst 2836.

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9. Sonnichsen, D. et al. *Pharmacokinetics (PK) and pharmacodynamics (PD) of the farnesyltransferase (FT) inhibitor BMS-214662 in patients with advanced solid tumors*. Proc Am Soc Clin Oncol 2000, 19: Abst 691.

ISIS-25513

288159

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is:
5'-GGTTCAGTGTGCGCCCGT-3', in which the central ten nucleotides are 2'-deoxynucleotides, the last four nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethyl nucleotides and the cytidines in positions 15 and 16 are 2'-*O*-methoxyethyl-5-methylcytidines

ACTION – Antisense chimeric phosphorothioate oligonucleotide targeted to nucleic acids encoding human RhoG, a member of the Rho subfamily of small GTPases, potentially useful for modulating RhoG expression and for the treatment of diseases associated with RhoG expression, particularly hyperproliferative conditions such as cancer. Compound inhibited RhoG mRNA levels by 82% at 150 nM in human cells. Other exemplified antisense oligonucleotides include the following:

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is:
5'-GGGTCCAACCTTGGCTTG-3', in which the central ten nucleotides are 2'-deoxynucleotides, the last four nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethyl nucleotides and the cytidine in position 15 is 2'-*O*-methoxyethyl-5-methylcytidine

ISIS-25534 [288160]

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is:
5'-GTCAGCAAATGCGGTAAGG-3', in which the central ten nucleotides are 2'-deoxynucleotides, the last four nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethyl nucleotides and the cytidine in position 3 is 2'-*O*-methoxyethyl-5-methylcytidine

ISIS-25543 [288161]

SOURCE – Isis Pharmaceuticals.

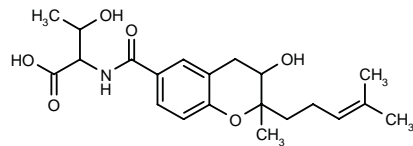
REFERENCES

1. Cowsert, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of RhoG expression*. WO 0018784.

ANGIOGENESIS INHIBITORS

288566

N-[3-Hydroxy-2-methyl-2-(4-methyl-3-pentenyl)-3,4-dihydro-2*H*-1-benzopyran-6-ylcarbonyl]-DL-threonine



C21 H29 N O6; Mol wt: 391.4611

ACTION – An inhibitor of ICAM-1/LFA-1 (intracellular adhesion molecule-1/lymphocyte function-associated antigen-1)-mediated cell adhesion isolated from a culture broth of *Streptomyces* sp. Mer-88 (FERM P-16829). Compound gave 91.7% inhibition of ICAM-1/LFA-1 binding at a concentration of 2500 µg/ml and inhibited T-cell leukemia SKW-3 cell adhesion to ICAM-1 by 38.4 ± 27.5% at 1000 µg/ml.

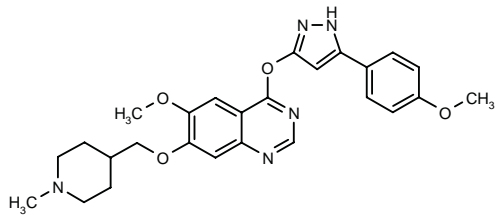
SOURCES – Daiichi Pharmaceutical; Mercian.

REFERENCES

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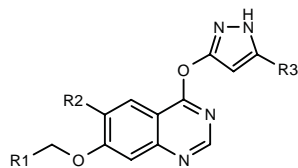
288993

6-Methoxy-4-[5-(4-methoxyphenyl)-1*H*-pyrazol-3-yloxy]-7-(1-methylpiperidin-4-ylmethoxy)quinazoline



C26 H29 N5 O4; Mol wt: 475.5461

ACTION – Potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinase, useful for the treatment of diseases associated with angiogenesis and/or increased vascular permeability such as cancer and rheumatoid arthritis. It is particularly expected to inhibit the growth of VEGF-related primary and recurrent solid tumors including certain tumors of the colon, breast, prostate, lung, vulva and skin. Other specifically claimed quinazoline derivatives are:



Compound	R1	R2	R3	Formula
288994	4-Me-1-Piz-CH2CH2	OMe	4-MeO-Ph	C27H32N6O4
288995	CH2OCH2CH2OMe	OMe	Ph	C23H24N4O5

288996	4-morpholinyl-CH2CH2	OMe	3-furyl	C23H25N5O5
288997	4-morpholinyl-CH2CH2	OMe	Ph	C25H27N5O4
288998	1-imidazolyl-CH2	OMe	Ph	C23H20N6O3
288999	4-morpholinyl-CH2CH2	OMe	4-Cl-Ph	C25H26ClN5O4
289000	4-Me-1-Piz-CH2CH2	OMe	Ph	C26H30N6O3
289001	CH2OMe	OMe	Ph	C21H20N4O4
289002	1,2,3-triazolyl-1-yl-CH2	OMe	4-MeO-Ph	C23H21N7O4
289003	1-(MeSO2CH2CH2)-4-Pip	OMe	4-MeO-Ph	C26H33N5O6S
289004	CH2OMe	H	Ph	C20H18N4O3
289005	4-morpholinyl-CH2CH2	OMe	2-F-Ph	C25H26FN5O4
289006	4-morpholinyl-CH2CH2	OMe	3-NO2-Ph	C25H26N6O6
289007	4-morpholinyl-CH2CH2	OMe	4-NO2-Ph	C25H26N6O6
289008	4-morpholinyl-CH2CH2	OMe	4-Pyr	C24H26N6O4
289009	4-morpholinyl-CH2CH2	OMe	4-F-Ph	C25H26FN5O4
289010	CH2OMe	OMe	4-MeO-Ph	C22H22N4O5

SOURCE – AstraZeneca.

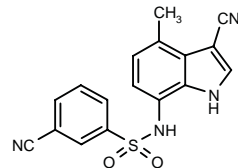
REFERENCES

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ER-68203-00

287632

3-Cyano-*N*-(3-cyano-4-methyl-1*H*-indol-7-yl)benzene-sulfonamide



C17 H12 N4 O2 S; Mol wt: 336.3738

ACTION – Angiogenesis inhibitor proven to inhibit tube formation induced by either FGF-2 or VEGF in a rat aorta matrix angiogenesis model. Compound was also seen to arrest the cell cycle at the G1 phase and to inhibit the proliferation of human umbilical vein endothelial cells (HUVEC), as well as downregulating the levels of integrin α₂ expression on the cell surface of both HUVEC and human microvascular vein endothelial cells (HMVEC). In *in vivo* studies, compound given orally was shown to reduce tumor-induced vascularization in a mouse angiogenesis model and to exert antitumor effects against several human tumor xenografts (colon, pancreatic, etc.) which were resistant to the compound in *in vitro* proliferation assays. In particular, it was able to completely suppress the growth of pancreatic cancer KP-1 tumors upon daily administration, to significantly suppress the formation of lung metastatic nodules in the breast MDA-MB-435 metastatic xenograft model and to completely inhibit the growth of paclitaxel-resistant tumors. Immuno-histochemical experiments demonstrated a significant reduction in intratumor microvessel density. No accumulative toxicity was seen in mice.

SOURCE – Eisai.

REFERENCES

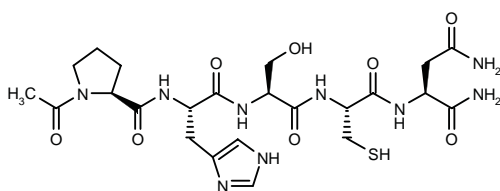
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2. Semba, T. et al. *A novel angiogenesis inhibitor ER-68203-00, II. Anti-angiogenesis potency and therapeutic efficacy in tumor xenograft models.* Proc Amer Assoc Cancer Res 2000, 41: Abst 4094.

OTHER ONCOLYTIC DRUGS

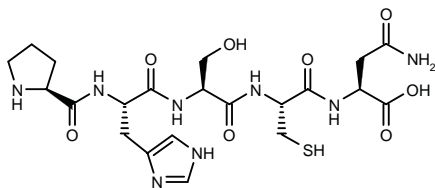
284918²

N-Acetyl-L-prolyl-L-histidyl-L-seryl-L-cysteiny-L-asparaginamide



C23 H35 N9 O8 S; Mol wt: 597.6505

ACTION – Potent antineoplastic and antimetastatic agent, the acetylated and amidated derivative of the PHSCN sequence of plasma fibronectin [284920]. In human and rat cultured prostate cancer cell lines, compound was effective in inhibiting PHSRN- and serum-induced invasion of human prostate carcinoma DU 145 and normal human prostate cells. *In vivo*, compound was effective in preventing metastatic prostate cancer in rats bearing MLL tumors when treatment began 1 day after MLL cell injection; it reduced the growth of primary MLL tumors by more than 2,000-fold and the density of the vasculature by more than 10-fold during the first 16 days of growth in rats, although subsequent tumor growth occurred. The effects of systemic treatment of compound could be attributable to a direct antiinvasive effect via the $\alpha_5\beta_1$ receptor expressed on rat endothelial cells and on the surface of MLL tumor cells. It also prevented the development of lung metastases when administered following surgical removal of the primary tumor. Potentially useful for the postsurgical treatment of extensive prostate cancer metastases.



284920^{1,2}; C21 H32 N8 O8 S

SOURCE – University of Michigan, Ann Arbor, MI (US).

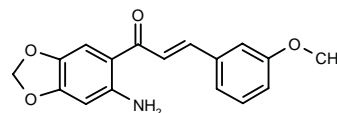
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2. Livant, D.L. et al. *Anti-invasive, antitumorigenic, and antimetastatic activities of the PHSCN sequence in prostate carcinoma.* Cancer Res 2000, 60(2): 309.

288879

1-(6-Amino-1,3-benzodioxol-5-yl)-3-(3-methoxyphenyl)-2(E)-propen-1-one



C17 H15 N O4; Mol wt: 297.3085

ACTION – Antineoplastic agent, a 2'-amino chalcone with high cytotoxic activity against a panel of human tumor cell lines including nasopharyngeal epidermoid carcinoma KB (IC_{50} = 0.52 μ g/ml), osteosarcoma HOS (IC_{50} = 2.4 μ g/ml), melanoma SK-MEL-2 (2.3 μ g/ml), ileocecal carcinoma HCT-8 (IC_{50} = 1.5 μ g/ml), breast cancer MCF-7 (IC_{50} = 0.48 μ g/ml), lung carcinoma A549 (IC_{50} = 0.45 μ g/ml), glioblastoma U87-MG (IC_{50} = 8 μ g/ml) and ovarian cancer 1A9 cells (IC_{50} = 0.35 μ g/ml). Compound was also active against multidrug-resistant nasopharyngeal carcinoma KB-VIN cells (IC_{50} = 0.3 μ g/ml).

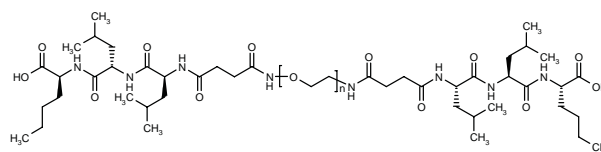
SOURCE – University of North Carolina, Chapel Hill, NC (US).

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288891

(Polyoxyethylene)₁₉₋₂₅-[NH-CO-(CH₂)₂-CO-Leu-Leu-Nle-H]₂



C44 H78 N8 O12(C2 H4 O)_n; Mol wt: 955.1968

ACTION – Proteasome inhibitor, a specifically claimed compound from a series of bivalent derivatives comprising two head groups and a spacer group, particularly polyethylene glycol. Claimed for reducing the rate of intracellular protein breakdown, inhibiting NF- κ B activity and NF- κ B-dependent cell adhesion, reducing p53 and cyclin degradation, as well as for inhibiting inflammatory responses, HIV replication and cancer cell growth.

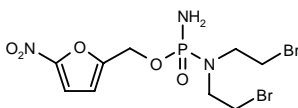
SOURCE – Max-Planck-Gesellschaft, München (DE).

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1. Ditzel, L. et al. (Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V.) *Bivalent inhibitors of the proteasome.* EP 0995757.

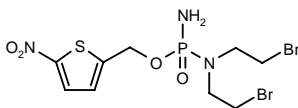
289144

N,N-Bis(2-bromoethyl)(5-nitro-2-furanyl)methylphosphorodiamidate



C9 H14 Br2 N3 O5 P; Mol wt: 435.0076

ACTION – Antineoplastic agent with cytotoxic activity against the NCI panel of human tumor cell lines, with a mean LC₅₀ value of 25 μ M. It exhibited strong activity against murine melanoma B16 (LC₉₉ = 2.0 μ M), human breast cancer MCF-7 (LC₉₉ = 4.5 μ M) and 4-hydroperoxycyclophosphamide-resistant MCF-7 cells (LC₉₉ = 2.9 μ M). Compound also reduced human colon cancer HT-29 cell survival under both aerobic and hypoxic conditions (LC₉₉ = 1.8 and 0.22 μ M, respectively). Selected for further evaluation. Another nitroheterocyclic phosphoramidate is:



289143: C9 H14 Br2 N3 O4 P S

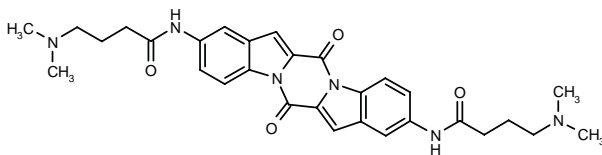
SOURCES – Purdue University, West Lafayette, IN (US); University of Rochester Medical Center, Rochester, NY (US); University of Wisconsin-Madison, Madison, WI (US).

REFERENCES

1. Borch, R.F. et al. *Synthesis and evaluation of nitroheterocyclic phosphoramidates as hypoxia-selective alkylating agents*. J Med Chem 2000, 43(11): 2258.

289869

4,4'-Bis(dimethylamino)-*N,N'*-(6,13-dioxo-6*H*,13*H*-diindolo[1,2-*a*:1',2'-*d'*]pyrazine-2,9-diyl)bis(butanamide)



C30 H34 N6 O4; Mol wt: 542.6366

ACTION – Potent cytotoxic agent from a novel class of diketopiperazines, giving an IC₅₀ of 34 nM against murine leukemia L1210 cells and showing significant affinity for DNA.

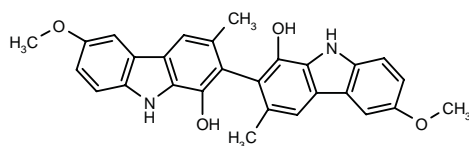
SOURCE – Scripps Research Institute, La Jolla, CA (US).

REFERENCES

1. Boger, D.L. et al. *A new class of highly cytotoxic diketopiperazines*. Bioorg Med Chem Lett 2000, 10(10): 1019.

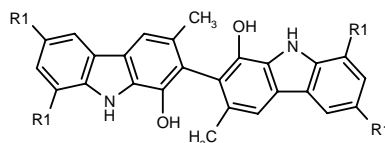
289871^{4,6}

6,6'-Dimethoxy-3,3'-dimethyl[2,2'-bi-9*H*-carbazole]-1,1'-diol



C28 H24 N2 O4; Mol wt: 452.5076

ACTION – Cytotoxic agent, a bicarbazole analogue of clausenamine A, a natural compound isolated from the stem and root bark of the Chinese plant *Clausena excavata*. Compound exhibited broad-spectrum cytotoxic activity against human cancer cells (GI₅₀ = 3-5 μ M), with particularly notable activity against human leukemia HL-60 cells (GI₅₀ = 0.032 μ M). Other related compounds are:



Compound	R1	Formula
O-Demethylmurrayafoline A [289870] ^{1-3,6}	H	C ₂₆ H ₂₀ N ₂ O ₂
Clausenamine A [289872] ^{5,6}	OMe	C ₃₀ H ₂₈ N ₂ O ₆

SOURCES – Chinese Academy of Sciences, Beijing, (CN); National Cancer Institute, Bethesda, MD (US).

REFERENCES

1. Bringmann, G. et al. *Antiplasmodial activity of mono- and dimeric carbazoles*. Planta Med 1998, 64(1): 54.

2. Ito, C. et al. *Alkaloid constituents of Murraya koenigii. Isolation and structural elucidation of novel binary carbazolequinones and carbazole alkaloids*. Chem Pharm Bull 1993, 41(12): 2096.

3. Knoelker, H.J. et al. *Transition metal complexes in organic synthesis: Part 31. A novel molybdenum-mediated synthesis of carbazole derivatives. Application to the total synthesis of mukonal and 1,1'-bis (2-hydroxy-3-methylcarbazole)*. Synlett 1996, (8): 737.

4. Lin, G. and Zhang, A. *The first synthesis of optically pure biscarbazoles and determination of their absolute configurations*. Tetrahedron Lett 1999, 40(2): 341.

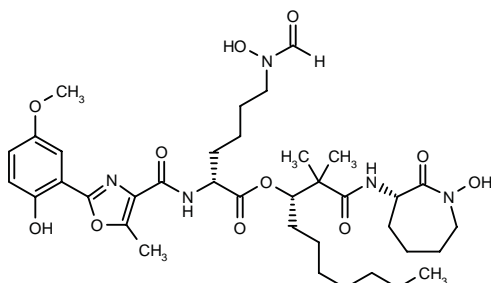
5. Wu, T.-S. et al. *Carbazole-pyranocoumarin dimer and binary carbazole alkaloid from Clausena excavata*. Tetrahedron Lett 1996, 37(43): 7819.

6. Zhang, A. and Lin, G. *The first synthesis of clausenamine-A and cytotoxic activities of three biscarbazole analogues against cancer cells*. Bioorg Med Chem Lett 2000, 10(10): 1021.

AMAMISTATIN A^{1,2}

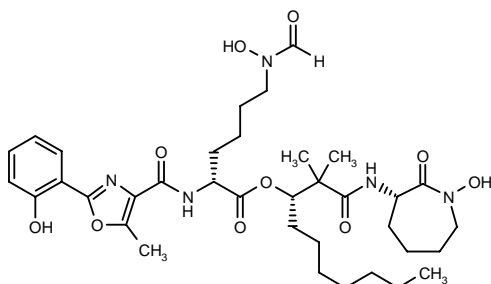
289461

6-(*N*-Formyl-*N*-hydroxyamino)-2(*R*)-[2-(2-hydroxy-5-methoxyphenyl)-5-methyloxazol-4-ylcarboxamido]hexanoic acid 1(*S*)-[2-[1-hydroxy-2-oxoperhydroazepin-3(*S*)-ylamino]-1,1-dimethyl-2-oxoethyl]octyl ester



C37 H55 N5 O11; Mol wt: 745.8655

ACTION – Antineoplastic agent isolated from ray fungal strain SCRC-A2359 (FERM P-16804) and subsequently synthesized, proven to inhibit the proliferation of leukemia P388 cells with an IC₅₀ value of 15 ng/ml. Another compound isolated from the same source is:



Amamistatin B [289462]:¹ C36 H53 N5 O10

SOURCE – Sagami.

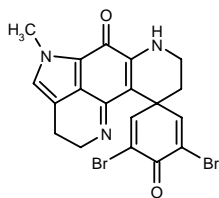
REFERENCES

1. Tsuji, T. et al. (Sagami Chemical Research Center) *Lipopeptide cpds. having anti-tumor activity*. JP 2000095781.
2. Yokokawa, F. et al. *Total synthesis of amamistatin A, an antiproliferative linear peptide from an actinomycete*. Tetrahedron 2000, 56(19): 3027.

DISCORHABDIN P

288965

3,5-Dibromo-5'-methyl-2',3',5',7',8',9'-hexahydro-spiro[2,5-cyclohexadiene-1,10'(6'*H*)-pyrrolo-[4,3,2-*de*][1,7]phenanthroline]-4,6'-dione



C19 H15 Br2 N3 O2; Mol wt: 477.1545

ACTION – Immunomodulating and antineoplastic agent isolated from a marine sponge of the genus *Batzella*. Compound was found to inhibit caspase 3 (CPP32; IC₅₀ = 0.37 µg/ml) and calcineurin (IC₅₀ = 0.55 µg/ml using enzyme derived from bovine brain), as well as the growth of murine leukemia P388 (IC₅₀ = 0.025 µg/ml) and human lung adenocarcinoma A549 cells (IC₅₀ = 0.41 µg/ml).

SOURCE – Harbor Branch Oceanographic Institution, Fort Pierce, FL (US).

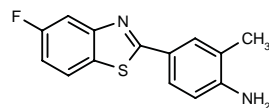
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1. Gunaskera, S.P. et al. (Harbor Branch Oceanographic Institution, Inc.) *Discorhabdin cpds. and methods of use*. US 6057333.
2. Gunasekera, S.P. et al. *Discorhabdin P, a new enzyme inhibitor from a deep-water Caribbean sponge of the genus Batzella*. J Nat Prod 1999, 62(1): 173.

5F-203

287652

4-(5-Fluorobenzothiazol-2-yl)-2-methylphenylamine



C14 H11 F N2 S; Mol wt: 258.3189

ACTION – Antineoplastic agent from a series of fluorinated benzothiazoles with strong cytotoxic activity *in vitro* against human carcinoma cell lines including non-small cell lung cancer H226 and H460 cell lines (GI₅₀ < 10 nM). Compound had no significant toxicity in primary cultures of human hepatocytes and exhibited significant activity *in vivo* in the estrogen receptor-negative breast cancer MT-1 xenograft model when administered at a dose of 15 mg/kg i.p.

SOURCES – National Cancer Institute, Bethesda, MD (US); University of Nottingham, Nottingham (GB).

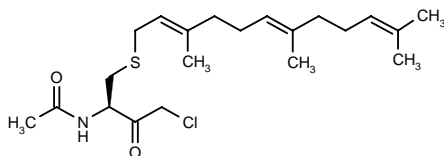
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1. Alley, M.C. et al. *Pharmacologic evaluations of fluorinated 2-(4-amino phenyl) benzothiazole analogs with unique anticancer activities*. Proc Amer Assoc Cancer Res 2000, 41: Abst 5166.
2. Bradshaw, T.D. et al. *Antitumor activity of fluorinated 2-(4-aminophenyl)benzothiazoles*. Proc Amer Assoc Cancer Res 2000, 41: Abst 4885.
3. Hutchinson, I. et al. *Antitumor benzothiazoles.9. The regiospecific synthesis of 5- and 7-monosubstituted and 5,6-disubstituted 2-arylbenzothiazoles*. Tetrahedron Lett 2000, 41(3): 425.
4. Westwell, A.D. et al. *Synthesis of fluorinated 2-(4-aminophenyl)benzothiazoles: A new generation of potent and selective antitumor agents*. Proc Amer Assoc Cancer Res 2000, 41: Abst 4884.

HI-368

288619

N-[3-Chloro-2-oxo-1(*R*)-[(2*E*,6*E*)-3,7,11-trimethyl-2,6,10-dodecatrienylsulfanylmethyl]propyl]acetamide



C₂₁ H₃₄ Cl N O₂ S; Mol wt: 400.0236

M.p. 59-61 °C.

ACTION – Antineoplastic agent active against human acute lymphoblastic leukemia (ALL) MOLT-3 cells (IC₅₀ = 1.4 μM), and also against p53-deficient ALL Nalm-6 cells (IC₅₀ = 3.0 μM) previously shown to be resistant to multiple chemotherapeutic agents including topoisomerase I and II inhibitors, vincristine and paclitaxel.

SOURCE – Parker Hughes Institute, Roseville, MN (US).

REFERENCES

1. Uckun, F.M. et al. (Wayne Hughes Institute) *Alkyl ketones as potent anti-cancer agents*. WO 0000469.

2. Perrey, D.A. et al. *Cysteine chloromethyl and diazomethyl ketone derivatives with potent anti-leukemic activity*. Bioorg Med Chem Lett 2000, 10(6): 547.

ISIS-16834

288805

20-Mer antisense oligonucleotide whose sequence is: 5'-CCTCGTGGTGCGCCTTCACG-3', in which the first and last five internucleotide linkages at the 5'- and 3'-ends are phosphodiester linkages, the central nine internucleotide linkages are phosphorothioate linkages, the central eight nucleotides are 2'-deoxynucleotides, the last six nucleotides at the 5'- and 3'-ends are 2'-*O*-methoxyethyl nucleotides and the cytidines in positions 1, 2, 4, 17 and 19 are 2'-*O*-methoxyethyl-5-methylcytidines

ACTION – Antisense oligonucleotide targeted to nucleic acids encoding the TNF receptor-associated factor (TRAF) that modulates TRAF-2, a member of the TRAF family. Concentration-dependent reduction in TRAF-2 mRNA levels in HMVEC cells with ISIS-16384 was observed in the range 1-100 nM, with an IC₅₀ of about 10 nM and 97% inhibition at 100 nM. The compound is expected to be useful in the treatment of hyperproliferative and inflammatory diseases. Another representative oligonucleotide is:

20-Mer antisense oligonucleotide whose sequence is: 5'-ACATATTTCCCGTGGCTTGT-3', in which the first and last five internucleotide linkages at the 5'- and 3'-ends are phosphodiester linkages, the central nine internucleotide linkages are phosphorothioate linkages, the central eight nucleotides are 2'-deoxynucleotides, the last six nucleotides at the 5'- and 3'-ends are 2'-*O*-methoxyethyl nucleotides and the cytidines in positions 2 and 16 are 2'-*O*-methoxyethyl-5-methylcytidines

ISIS-15910 [288806]

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Baker, B.F. et al. (Isis Pharmaceuticals, Inc.) *Antisense modulation of expression of tumor necrosis factor receptor-associated factors (TRAFs)*. WO 0020435.

ISIS-19387

288200

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is:

5'-TTCTCCACCAAACAAGTT-3', in which the central ten nucleotides are 2'-deoxynucleotides, the last four nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethyl nucleotides and the cytidine in position 3 is 2'-*O*-methoxyethyl-5-methylcytidine

ACTION – Antisense chimeric phosphorothioate oligonucleotide targeted to nucleic acids encoding human CD71, also known as the transferrin receptor, which mediates the uptake of circulating iron-transferrin complexes into cells and has been shown to be an essential factor for cell growth. Compound inhibited CD71 mRNA levels by 78% at 150 nM in human cells. Potentially useful for modulating CD71 expression and for the treatment of diseases associated with CD71 expression, particularly hyperproliferative conditions such as cancer. Other exemplified antisense oligonucleotides include the following:

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:

5'-ACGCCAGACTTTGCTGAG-3'

ISIS-18814 [288201]

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:

5'-TTGGCTTCTGGTCCCCTC-3'

ISIS-18854 [288202]

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:

5'-TTTGGCTGACGGCTGTTT-3'

ISIS-18859 [288203]

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Bennett, C.F. and Cowser, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of CD71 expression*. WO 0018785.

ISIS-22783

288795

20-Mer antisense phosphorothioate fully 2'-methoxyethoxy substituted oligonucleotide whose sequence is: CTGGATCCAAGGCTCTAGGT

ACTION – Antisense oligonucleotide targeted to nucleic acids encoding the polypeptide bcl-x, particularly the apoptosis-inhibiting isoform bcl-xl, proven to reduce bcl-xl mRNA levels to 35% of controls while markedly increasing bcl-xs (the short form of human bcl-x that inhibits bcl-2 function and thereby promotes programmed cell death) mRNA levels to 620% of controls in A549 cells. Similar bcl-xl/xs ratios were observed in other cell lines such as human embryonic kidney carcinoma 293T, human melanoma C8161 and HeLa cells. ISIS-22783 was found to sensitize A549 cells to apoptotic stimuli (UV irradiation or cytotoxic chemotherapeutic drug), increasing the number of apoptotic cells.

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Bennett, C.F. et al. (Isis Pharmaceuticals, Inc.) *Antisense modulation of bcl-x expression*. WO 0020432.

ISIS-23722

288162

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is: 5'-TGTGCTATTCTGTGAATT-3', in which the central ten nucleotides are 2'-deoxynucleotides and the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides

ACTION – Antisense chimeric phosphorothioate oligonucleotide targeted to nucleic acids encoding human survivin, a member of the IAP (inhibitor of apoptosis) caspase inhibitor family which is overexpressed in cancer and has been shown to play a role in cell cycle regulation. Compound inhibited survivin mRNA levels by 80% at 150 nM in human cells. Other exemplified antisense oligonucleotides include the following:

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is: 5'-CGATGGCACGGCGCACTT-3'

ISIS-23665 [288164]

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is: 5'-CGATGGCACGGCGCACTT-3', in which the central ten nucleotides are 2'-deoxynucleotides, the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides and the cytidines in positions 1 and 16 are 2-O-methoxyethyl-5-methylcytidines

ISIS-23705 [288165]

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Bennett, C.F. et al. (Isis Pharmaceuticals, Inc.) *Antisense modulation of survivin expression*. WO 0018781.

ISIS-23905

288204

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is: 5'-ACATCTGGCCTGTTCCCA-3'

ACTION – Antisense phosphorothioate oligodeoxynucleotide targeted to nucleic acids encoding human RIP-1 (also known as RalBP1 or RLIP), a GTPase-activating protein thought to be associated with hyperproliferative conditions such as cancer. Compound inhibited RIP-1 mRNA levels by 44% at 150 nM in human cells. Other exemplified antisense oligonucleotides include the following:

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is: 5'-GTGCATCAGGTTGCCCTT-3', in which the central ten nucleotides are 2'-deoxynucleotides, the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides and the cytidines in positions 4, 15 and 16 are 2'-O-methoxyethyl-5-methylcytidines
ISIS-23937 [288205]

18-Mer chimeric antisense phosphorothioate oligonucleotide whose sequence is: 5'-ATTCGCTTCCCAGCAGAG-3', in which the ten central nucleotides are 2'-deoxynucleotides, the last four nucleotides flanking the 5'- and 3'-ends are 2'-O-methoxyethyl nucleotides and the cytidine in position 4 is 2'-O-methoxymethyl-5-methylcytidine

ISIS-23946 [288206]

SOURCE – Isis Pharmaceuticals.

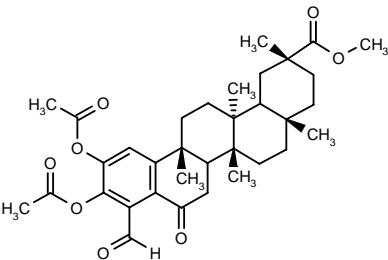
REFERENCES

1. Bennett, C.F. and Cowser, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of RIP-1 expression*. WO 0018786.

MACROCARPIN A ACETATE

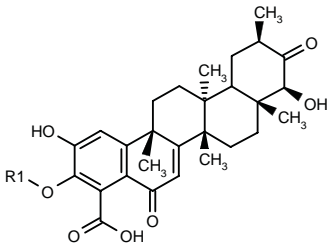
288894

(2*R*,4*aS*,6*aR*,12*bR*,14*aS*)-10,11-Diacetoxy-9-formyl-2,4*a*,6*a*,12*b*,14*a*-pentamethyl-8-oxo-1,2,3,4,4*a*,5,6,6*a*,6*b*,7,8,12*b*,13,14,14*a*,14*b*-hexadecahydropicene-2-carboxylic acid methyl ester

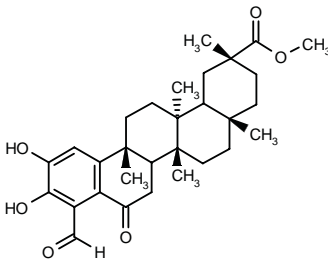


C34 H44 O8; Mol wt: 580.7136

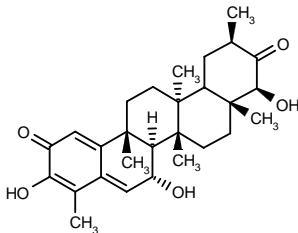
ACTION – Antineoplastic agent, the acetyl derivative of a natural compound extracted from the roots of the Peruvian plant *Maytenus macrocarpa*. It exhibited cytotoxic activity against cultured cell lines including murine lymphoma P388D1, human lung carcinoma A549, human colon carcinoma HT-29 and human melanoma SK-MEL-28 (IC₅₀ = 0.4 µM). The natural compounds extracted from this plant are:



Compound	R1	Formula
Macrocarpin B [288895]	H	C ₂₈ H ₃₄ O ₇
Macrocarpin C [288896]	Me	C ₂₉ H ₃₆ O ₇



Macrocarpin A [288893]: C₃₀ H₄₀ O₆



Macrocarpin D [288897]: C₂₈ H₃₈ O₅

SOURCES – Instituto Biomar; Universidad de La Laguna, La Laguna (ES); PharmaMar.

REFERENCES

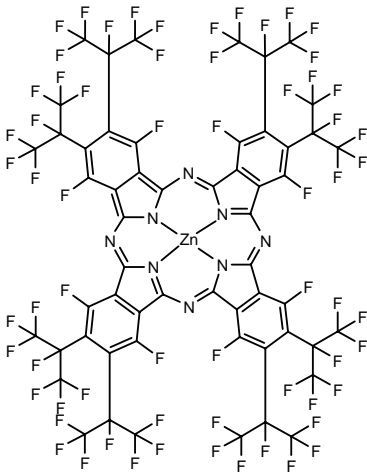
1. Chávez, H. et al. *Macrocarpins A-D, new cytotoxic nor-triterpenes from Maytenus macrocarpa*. Bioorg Med Chem Lett 2000, 10(8): 759.

PHOTOSENSITIZERS

ZnPcF64

288941

[1,4,8,11,15,18,22,25-Octafluoro-2,3,9,10,16,17,23,24-octakis(perfluoroisopropyl)phthalocyaninato(2-)-N²⁹,N³⁰,N³¹,N³²]zinc



C₅₆ F₆₄ N₈ Zn; Mol wt: 2065.9340

ACTION – Agent for the photodynamic therapy of cancer, as well as for the photoinactivation of viruses in blood, proven to produce complete tumor necrosis when given at a dose of 1 µmol/kg i.v. to mice bearing EMT-6 tumors followed by red light irradiation.

SOURCE – Brown University, Providence, RI (US).

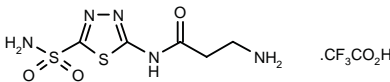
REFERENCES

1. Gorun, S.M. (Brown University) *Subst. perhalogenated phthalocyanines*. WO 0021965.

OCULAR MEDICATIONS

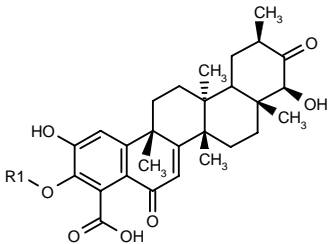
287858¹⁻⁶

N-[5-(Aminosulfonyl)-1,3,4-thiadiazol-2-yl]-β-alanine trifluoroacetate

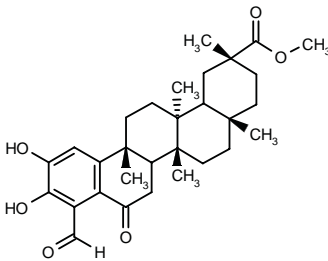


C₅ H₉ N₅ O₃ S₂ . C₂ H₃ F₃ O₂; Mol wt: 365.3120

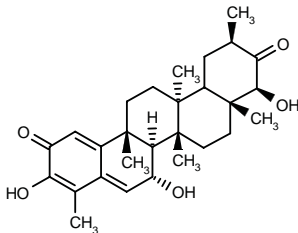
ACTION – Antineoplastic agent, the acetyl derivative of a natural compound extracted from the roots of the Peruvian plant *Maytenus macrocarpa*. It exhibited cytotoxic activity against cultured cell lines including murine lymphoma P388D1, human lung carcinoma A549, human colon carcinoma HT-29 and human melanoma SK-MEL-28 (IC₅₀ = 0.4 µM). The natural compounds extracted from this plant are:



Compound	R1	Formula
Macrocarpin B [288895]	H	C ₂₈ H ₃₄ O ₇
Macrocarpin C [288896]	Me	C ₂₉ H ₃₆ O ₇



Macrocarpin A [288893]: C₃₀ H₄₀ O₆



Macrocarpin D [288897]: C₂₈ H₃₈ O₅

SOURCES – Instituto Biomar; Universidad de La Laguna, La Laguna (ES); PharmaMar.

REFERENCES

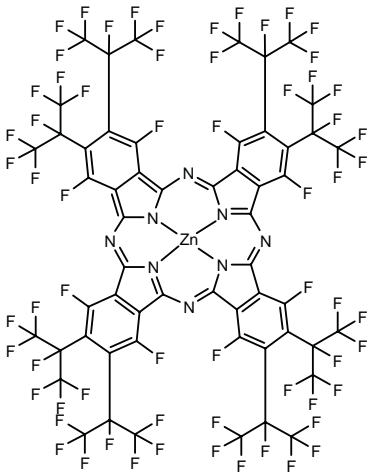
1. Chávez, H. et al. *Macrocarpins A-D, new cytotoxic nor-triterpenes from Maytenus macrocarpa*. Bioorg Med Chem Lett 2000, 10(8): 759.

PHOTOSENSITIZERS

ZnPcF64

288941

[1,4,8,11,15,18,22,25-Octafluoro-2,3,9,10,16,17,23,24-octakis(perfluoroisopropyl)phthalocyaninato(2-)-N²⁹,N³⁰,N³¹,N³²]zinc



C₅₆ F₆₄ N₈ Zn; Mol wt: 2065.9340

ACTION – Agent for the photodynamic therapy of cancer, as well as for the photoinactivation of viruses in blood, proven to produce complete tumor necrosis when given at a dose of 1 µmol/kg i.v. to mice bearing EMT-6 tumors followed by red light irradiation.

SOURCE – Brown University, Providence, RI (US).

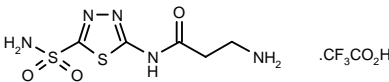
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1. Gorun, S.M. (Brown University) *Subst. perhalogenated phthalocyanines*. WO 0021965.

OCULAR MEDICATIONS

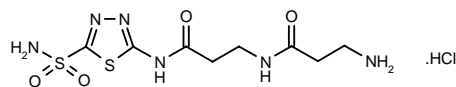
287858¹⁻⁶

N-[5-(Aminosulfonyl)-1,3,4-thiadiazol-2-yl]-β-alanine trifluoroacetate



C₅ H₉ N₅ O₃ S₂ . C₂ H₃ F₃ O₂; Mol wt: 365.3120

ACTION – Antiglaucoma agent, an inhibitor of carbonic anhydrase (CA; K_i = 455, 3 and 125 nM, respectively, against human CA I, human CA II and bovine CA IV). Compound possesses good water solubility (70 mM) and exhibited suitable lipid solubility, hydrophobicity and permeability across the cornea for acting as an efficient topical intraocular pressure (IOP)-lowering agent. When administered topically directly to the eye of normotensive and glaucomatous rabbits, compound at a concentration of 2% induced a marked and long-lasting decrease in IOP, superior to that of the clinically available dorzolamide. High levels of compound were found in the cornea, aqueous humor and ciliary processes 1 and 2 h after topical administration to the cornea. Another related compound is:



287859^{5,6}: C₈ H₁₄ N₆ O₄ S₂ . HCl

SOURCE – Università degli Studi di Firenze, Firenze (IT).

REFERENCES

1. Mincione, G. et al. *Carbonic anhydrase inhibitors. Part 79. Synthesis of topically acting sulfonamides incorporating GABA moieties in their molecule, with long-lasting intraocular pressure-lowering properties.* Eur J Pharm Sci 1999, 9(2): 185.

2. Scozzafava, A. et al. *Carbonic anhydrase inhibitors. Synthesis of water-soluble, topically effective intraocular pressure-lowering aromatic/heterocyclic sulfonamides containing cationic or anionic moieties. Is the tail more important than the ring?* J Med Chem 2000, 42(14): 2641.

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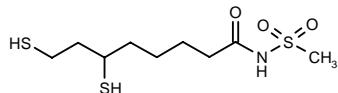
4. Scozzafava, A. et al. *Carbonic anhydrase inhibitors: Synthesis of water-soluble, aminoacyl/dipeptidyl sulfonamides possessing long-lasting intraocular pressure-lowering properties via the topical route.* J Med Chem 1999, 42(18): 3690.

5. Supuran, C.T. et al. *Carbonic anhydrase inhibitors - Part 78. Synthesis of water-soluble sulfonamides incorporating β -alanyl moieties, possessing long lasting intraocular pressure lowering properties via the topical route.* Eur J Med Chem 2000, 35(3): 309.

6. Supuran, C.T. et al. *Carbonic anhydrase inhibitors. Part 71. Synthesis and ocular pharmacology of a new class of water-soluble, topically effective intraocular pressure lowering sulfonamides incorporating picolinoyl moieties.* Eur J Pharm Sci 1999, 8(4): 317.

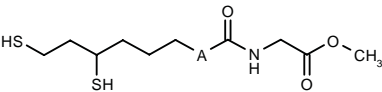
288824

N-(Methylsulfonyl)-6,8-disulfanyloctanamide



C₉ H₁₉ N O₃ S₃; Mol wt: 285.4511

ACTION – Anticataract agent found to potentiate the activity of glutathione reductase and to have anticataract properties in mice. Other exemplified dithiol derivatives include the following:



Compound	A	Formula
288826	-CH ₂ NH-	C ₁₁ H ₂₂ N ₂ O ₃ S ₂
288827	-CH ₂ -	C ₁₁ H ₂₁ NO ₃ S ₂

SOURCE – Sankyo.

REFERENCES

1. Fujita, T. and Yokoyama, T. (Sankyo Co., Ltd.) *Dithiol derivs.* JP 2000169443, WO 0020385.

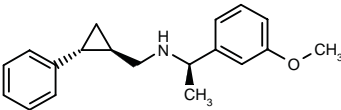
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

288937

1-(R)-(3-Methoxyphenyl)-N-[2(R)-phenylcycloprop-1(R)-ylmethyl]ethanamine

N-[1(R)-(3-Methoxyphenyl)ethyl]-N-[(1R,2R)-2-phenylcyclopropylmethyl]amine



C₁₉ H₂₃ N O; Mol wt: 281.3967

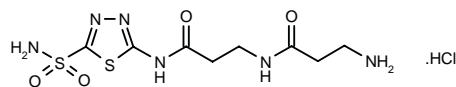
ACTION – Agent that binds to the calcium-sensing receptor and is thus expected to be useful for the treatment of diseases related to calcium imbalance and metabolism such as hyperparathyroidism, osteoporosis, Paget’s disease, hypercalcemia of malignancy, hypertension and renal osteodystrophy. Compound exhibited a CS₅₀ (potency is 50% of the calcium standard potency) value of 5.0 μ M when tested *in vitro* in a calcium mobilization assay in HEK 293 cells transfected with the calcium-sensing receptor found in the human parathyroid gland, and produced an 83.6% decrease in blood serum parathyroid hormone (PTH) levels in rats at 30 mg/kg p.o. A specifically claimed compound from a series of 1,2-disubstituted cyclopropanes.

SOURCE – Ortho-McNeil.

REFERENCES

1. Cohen, J.H. et al. (Ortho-McNeil Pharmaceutical, Inc.) *1,2-Disubstd. cyclopropanes.* WO 0021910.

ACTION – Antiglaucoma agent, an inhibitor of carbonic anhydrase (CA; K_i = 455, 3 and 125 nM, respectively, against human CA I, human CA II and bovine CA IV). Compound possesses good water solubility (70 mM) and exhibited suitable lipid solubility, hydrophobicity and permeability across the cornea for acting as an efficient topical intraocular pressure (IOP)-lowering agent. When administered topically directly to the eye of normotensive and glaucomatous rabbits, compound at a concentration of 2% induced a marked and long-lasting decrease in IOP, superior to that of the clinically available dorzolamide. High levels of compound were found in the cornea, aqueous humor and ciliary processes 1 and 2 h after topical administration to the cornea. Another related compound is:



287859^{5,6}: C₈ H₁₄ N₆ O₄ S₂ . HCl

SOURCE – Università degli Studi di Firenze, Firenze (IT).

REFERENCES

1. Mincione, G. et al. *Carbonic anhydrase inhibitors. Part 79. Synthesis of topically acting sulfonamides incorporating GABA moieties in their molecule, with long-lasting intraocular pressure-lowering properties.* Eur J Pharm Sci 1999, 9(2): 185.

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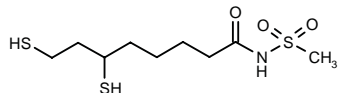
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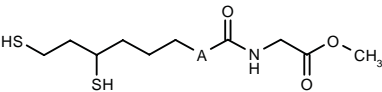
288824

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REFERENCES

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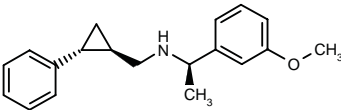
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

288937

1-(R)-(3-Methoxyphenyl)-N-[2(R)-phenylcycloprop-1(R)-ylmethyl]ethanamine

N-[1(R)-(3-Methoxyphenyl)ethyl]-N-[(1R,2R)-2-phenylcyclopropylmethyl]amine



C₁₉ H₂₃ N O; Mol wt: 281.3967

ACTION – Agent that binds to the calcium-sensing receptor and is thus expected to be useful for the treatment of diseases related to calcium imbalance and metabolism such as hyperparathyroidism, osteoporosis, Paget’s disease, hypercalcemia of malignancy, hypertension and renal osteodystrophy. Compound exhibited a CS₅₀ (potency is 50% of the calcium standard potency) value of 5.0 μ M when tested *in vitro* in a calcium mobilization assay in HEK 293 cells transfected with the calcium-sensing receptor found in the human parathyroid gland, and produced an 83.6% decrease in blood serum parathyroid hormone (PTH) levels in rats at 30 mg/kg p.o. A specifically claimed compound from a series of 1,2-disubstituted cyclopropanes.

SOURCE – Ortho-McNeil.

REFERENCES

1. Cohen, J.H. et al. (Ortho-McNeil Pharmaceutical, Inc.) *1,2-Disubstd. cyclopropanes.* WO 0021910.

4B4-6-21

288830

Human monoclonal antibody to parathyroid hormone-related protein

ACTION – Human monoclonal antibody to parathyroid hormone-related protein (PTHrP), with a dissociation constant (K_D) of 0.63 nM for PTHrP; it inhibited PTHrP-induced bone resorption *in vitro* in neonatal mouse parietal bone cultures with an IC_{50} of 4 µg/ml, as well as PTHrP-stimulated increases in cAMP levels in rat osteosarcoma UMR106 cells at 0.3 and 1 µg/ml. *In vivo*, it was found to significantly inhibit malignancy-associated hypercalcemia in mice bearing human oral squamous cell carcinoma HOSO at 3 mg/kg i.v.

SOURCE – Japan Tobacco.

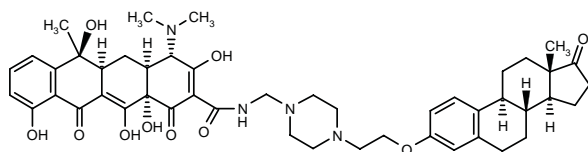
REFERENCES

1. Hori, N. et al. (Japan Tobacco Inc.) *Human monoclonal antibody to parathyroid hormone related protein*. JP 2000080100.

XW-630

288207

(4*S*,4*aS*,5*aS*,6*S*,12*aS*)-4-(Dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-*N*-[4-[2-[17-oxoestra-1,3,5(10)-trien-3-yloxy]ethyl]piperazin-1-ylmethyl]-1,11-dioxo-1,4,4*a*,5,5*a*,6,11,12*a*-octahydronaphthacene-2-carboxamide



C47 H58 N4 O10; Mol wt: 838.9932

ACTION – Agent for the treatment of bone disorders, particularly osteoporosis, a conjugate of tetracycline and estrone with estrogen-agonist activity (relative affinity for the estrogen receptor compared to estradiol = 0.011). Compound stimulated proliferation and enhanced inducible nitric oxide synthase (iNOS) activity and cGMP content in the human osteoblast-like cell line TE85. *In vivo* in ovariectomized osteoporotic rats, compound given orally at a dose of 2.5 mg/kg/day for 13 weeks increased bone mass and trabecular spatial architecture, as well as the stability and strength of bone; it stimulated bone formation and inhibited bone resorption without affecting the reproductive system. In a rabbit experimental fracture model, compound given by i.m. injection accelerated fracture healing.

SOURCE – West China University of Medical Sciences, Chengdu (CN).

REFERENCES

1. Li, D. et al. *Effects of the new compound XW630 on osteoblast*. J West China Univ Med Sci 1998, 29(4): 368.
2. Li, L. et al. *A biomechanical evaluation of the effects of XW630 on the healing of experimental fracture*. J Biomed Eng 1998, 15(1): 1.

3. Mo, Z.J. et al. *The estrogenic activities of 2-[3-estrone-*N*-ethyl-piperazine-methyl]tetracycline (XW630) - A new compound with anti-osteoporosis activity*. Acta Pharm Sin 1998, 33(9): 645.

4. Qiu, M. et al. *Investigation of tetracycline-estrone (XW630) effects on femoral trabecular structure in ovariectomized (OVX) rats: Bone histomorphometric study*. J Bone Miner Res 1999, 14(Suppl. 1): Abst F317.

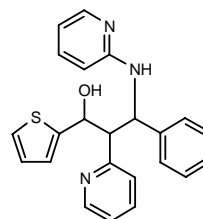
5. Sun, L. et al. *Effects of 2-[3-estrone-*N*-ethyl-piperazine-methyl]tetracycline (XW630) on osteoporosis in ovariectomized rats*. Acta Pharmacol Sin 2000, 21(3): 200.

6. Sun, L. et al. *Effects of XW630 on cell proliferation, iNOS activity, and cGMP content in human osteoblast-like cell line TE85*. Acta Pharmacol Sin 2000, 21(3): 261.

TREATMENT OF LIPOPROTEIN DISORDERS

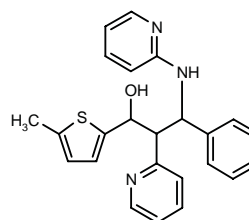
288698

3-Phenyl-2-(2-pyridyl)-3-(2-pyridylamino)-1-(2-thienyl)-1-propanol



C23 H21 N3 O S; Mol wt: 387.5049

ACTION – Hypolipidemic agent, a representative compound from a series of propanolamine derivatives with bile acid transport-inhibitory activity. Another exemplified compound is:



288699: C24 H23 N3 O S

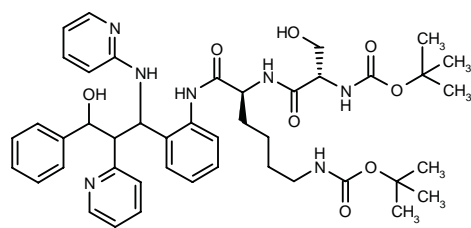
SOURCE – Aventis Pharma.

REFERENCES

1. Frick, W. et al. (Aventis Pharma Deutschland GmbH) *Propanolamine derivs. subst. with heterocyclic cpds., methods for their production, pharmaceutical compsns. containing said cpds. and the use thereof*. WO 0020410.

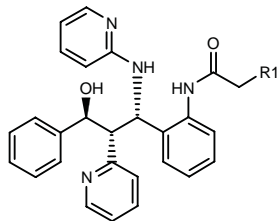
288700

N-(*tert*-Butoxycarbonyl)-L-seryl-*N*⁶-(*tert*-butoxycarbonyl)-L-lysine *N*-[2-[3-hydroxy-3-phenyl-2-(2-pyridyl)-1-(2-pyridylamino)propyl]phenyl]amide

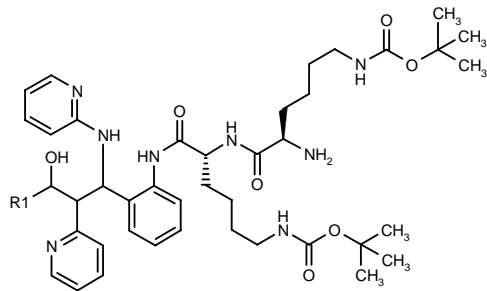


C44 H57 N7 O8; Mol wt: 811.9753

ACTION – Hypolipidemic agent, a representative compound from a series of substituted 1,3-diaryl-2-pyridin-2-yl-3-(pyridin-2-ylamino)propanol derivatives with bile acid transport-inhibitory activity. Other exemplified compounds include the following:



Compound	R1	Formula
288701	ethynyl-CH2	C ₃₀ H ₂₈ N ₄ O ₂
288702	2-pyrimidinyl-S	C ₃₁ H ₂₈ N ₆ O ₂ S



Compound	R1	Formula
288703	3,5-(Me)2-4-isoxazolyl	C ₄₆ H ₆₅ N ₉ O ₈
288704	2,5-(MeO)2-4-oxazolyl	C ₄₆ H ₆₅ N ₉ O ₈

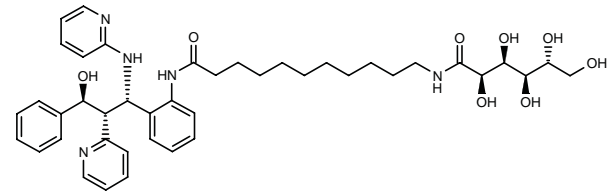
SOURCE – Aventis Pharma.

REFERENCES

1. Kirsch, R. et al. (Aventis Pharma Deutschland GmbH) *Substd. 1,3-diaryl-2-pyridine-2-yl-3-(pyridine-2-ylamino)-propanol derivs., methods for their production, pharmaceutical compsns. containing the same and their use.* WO 0020393.

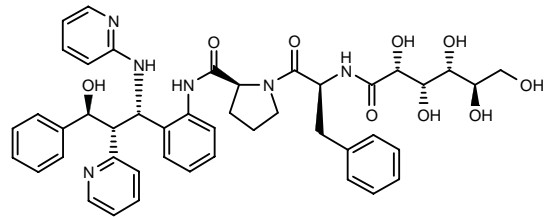
288705

N-[2-[3(*S*)-Hydroxy-3-phenyl-2(*R*)-(2-pyridyl)-1(*S*)-(2-pyridylamino)propyl]phenyl]-11-[2(*R*),3(*S*),4(*R*),5(*R*),6-pentahydroxyhexanamido]undecanamide

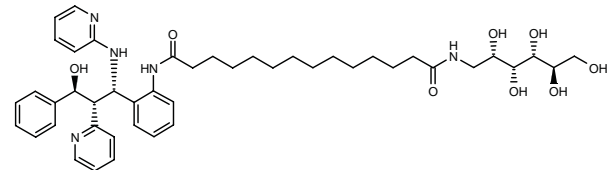


C42 H55 N5 O8; Mol wt: 757.9235

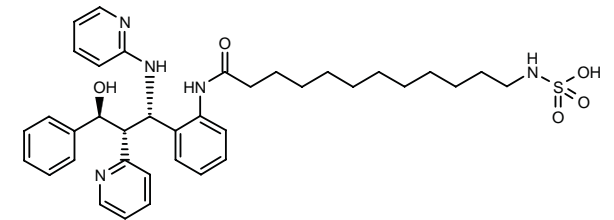
ACTION – Hypolipidemic agent, a representative compound from a series of aryl-substituted propanolamine derivatives with bile acid transport-inhibitory activity. Other exemplified compounds include the following:



288706: C45 H50 N6 O9



288708: C45 H61 N5 O8



288709: C37 H47 N5 O5 S

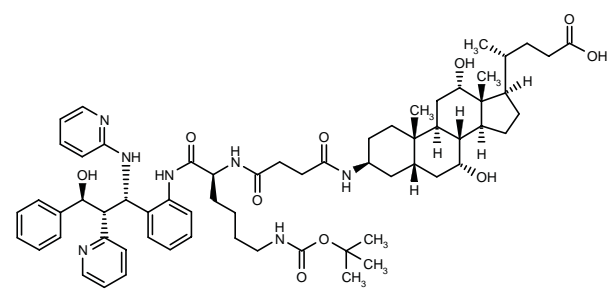
SOURCE – Aventis Pharma.

REFERENCES

1. Frick, W. et al. (Aventis Pharma Deutschland GmbH) *Aryl-substd. propanolamine derivs., methods for their production, medicaments containing said cpds. and their use.* WO 0020392.

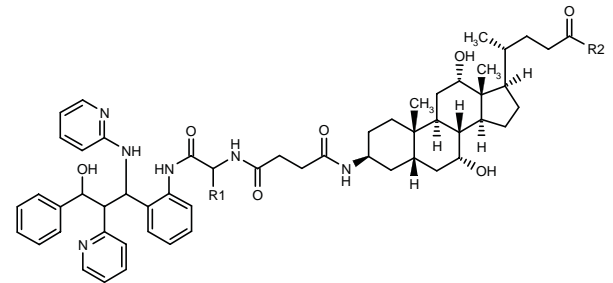
288730

3β-[4-[*N*⁶-(*tert*-Butoxycarbonyl)-1-[2-[3(*S*)-hydroxy-3-phenyl-2(*R*)-(2-pyridyl)-1(*S*)-(2-pyridylamino)propyl]-phenylamino]-*N*²-L-lysino]-4-oxobutyramido]-7α,12α-dihydroxy-5β-cholan-24-oic acid

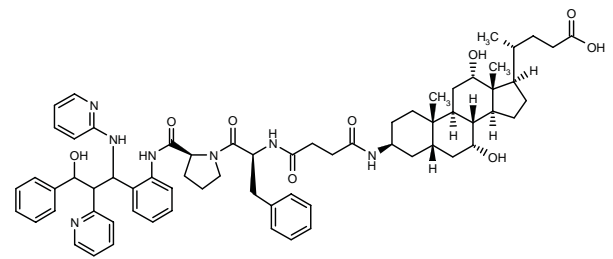


C64 H87 N7 O10; Mol wt: 1114.4300

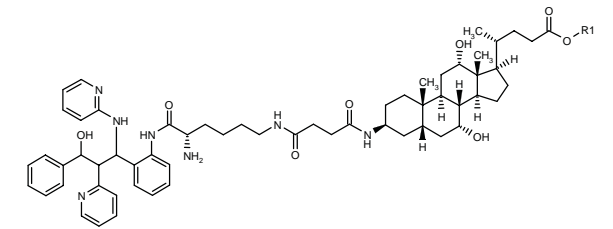
ACTION – Hypolipidemic agent, a representative compound from a series of propanolamine derivatives linked with a bile acid that act as bile acid transport inhibitors. Other exemplified compounds include the following:



Compound	R1	R2	Formula
288732	(<i>R</i>)- <i>t</i> -BuOCONH(CH ₂) ₄	OH	C ₆₄ H ₈₇ N ₇ O ₁₀
288733	(<i>R</i>)- <i>t</i> -BuOCONH(CH ₂) ₄	NHCH ₂ CH ₂ SO ₃ H	C ₆₆ H ₉₂ N ₈ O ₁₂ S
288743	(<i>S</i>)- <i>t</i> -BuOCONH(CH ₂) ₄	NHCH ₂ CO ₂ H	C ₆₆ H ₉₀ N ₈ O ₁₁



Compound	Isomer	Formula
288736	1 <i>S</i> ,2 <i>R</i> ,3 <i>S</i>	C ₆₇ H ₈₃ N ₇ O ₉
288740	1 <i>R</i> ,2 <i>S</i> ,3 <i>R</i>	C ₆₇ H ₈₃ N ₇ O ₉



Compound	R1	Formula
288738	Me	C ₆₀ H ₈₁ N ₇ O ₈
288739	H	C ₅₉ H ₇₉ N ₇ O ₈

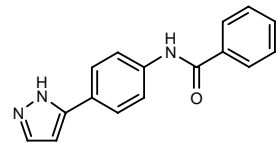
SOURCE – Aventis Pharma.

REFERENCES

1. Stengelin, S. et al. (Aventis Pharma Deutschland GmbH) *Propanolamine derivs. linked with bile acid used for treating disorders of the lipid metabolism*. WO 0020437.

289510

N-[4-(1*H*-Pyrazol-5-yl)phenyl]benzamide



C16 H13 N3 O; Mol wt: 263.2987

ACTION – Hypolipidemic agent found to decrease serum total cholesterol and triglyceride levels by 42 and 71%, respectively, at a dose of 25 mg/kg/day p.o. for 5 days in hypercholesterolemic hamsters. No toxicity or deaths were observed in rats given repeated oral doses of this compound of 100 mg/kg/day for 7 days.

SOURCE – Nippon Soda.

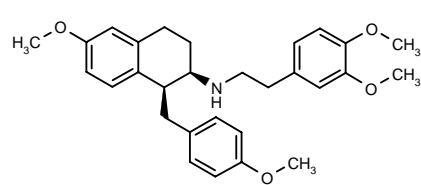
REFERENCES

1. Yamada, Y. et al. (Nippon Soda Co., Ltd.) *Phenylpyrazole cpds., their preparation method, and anti-hyperlipemia agents*. JP 2000109465.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

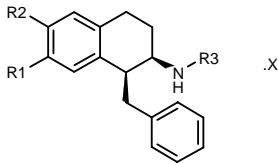
288680

cis-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-[6-methoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydronaphthalen-2-yl]amine



C29 H35 N O4; Mol wt: 461.5985

ACTION – Neuropeptide Y (NPY) Y₅ receptor antagonist, as demonstrated in a binding assay by 89% inhibition of [¹²⁵I]-PYY binding to human NPY Y₅ receptors expressed in HEK293 cells at a concentration of 3 μM. Claimed for the treatment of eating disorders, obesity, bulimia nervosa, diabetes, dyslipidemia, hypertension, memory loss, epileptic seizures, migraine, sleep disturbances, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea. A representative compound from a series of *N*-aralkylaminotetralins, wherein the following are also included:



Compound	R1	R2	R3	X	Formula
288681	H	OMe	3,4-(MeO)2-PhCH2CH2	HCl	C ₂₈ H ₃₃ NO ₃ .HCl
288682	H	H	3-indolyl-CH2CH2	fumarate	C ₂₇ H ₂₈ N ₂ .C ₄ H ₄ O ₄
288684	H	H	2-MeO-PhCO	HBr	C ₂₅ H ₂₅ NO ₂ .HBr
288685	OMe	H	3-indolyl-CH2CH2		C ₂₈ H ₃₀ N ₂ O
288686	H	OMe	4-MeO-PhCH2CH2		C ₂₇ H ₃₁ NO ₂

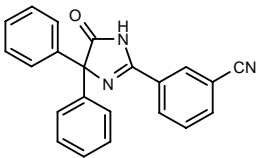
SOURCE – Ortho-McNeil.

REFERENCES

1. Dax, S.L. et al. (Ortho-McNeil Pharmaceutical, Inc.) *N*-Aralkylaminotetralins as ligands for the neuropeptide Y Y5 receptor. WO 0020376.

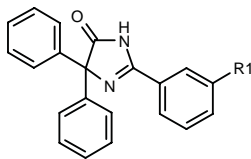
288786

3-(5-Oxo-4,4-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-benzonitrile



C22 H15 N3 O; Mol wt: 337.3805

ACTION – Selective antagonist at neuropeptide Y (NPY) Y₅ receptors that acts as an anorectic and is potentially useful for promoting weight loss in the treatment of obesity and eating disorders. Other exemplified phenyl-substituted imidazolone derivatives include the following:



Compound	R1	Formula
288787	CH2NH2	C ₂₂ H ₁₉ N ₃ O
288788	CH2Cl	C ₂₂ H ₁₇ ClN ₂ O
288790	NO2	C ₂₁ H ₁₅ N ₃ O ₃

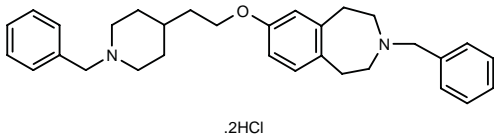
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Poindexter, G.S. et al. (Bristol-Myers Squibb Co.) *Imidazolone anorectic agents: II. Phenyl derivs.* US 6054590.

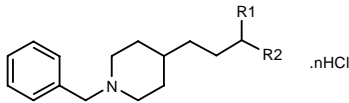
289421

3-Benzyl-7-[2-(1-benzylpiperidin-4-yl)ethoxy]-2,3,4,5-tetrahydro-1*H*-3-benzazepine dihydrochloride



C31 H38 N2 O . 2HCl; Mol wt: 527.5760

ACTION – Antiobesity agent with excellent thermogenesis-stimulating effects, shown to concentration-dependently increase cAMP levels in murine 3T3-L1 cells at 0.001-1 μM. Other compounds from this series of nitrogen-containing fused heterocycles include the following:



Compound	R1	R2	n	Formula
289425	H	7-(PhCH2)-6,7,8,9-tetrahydro-5 <i>H</i> -isoxazolo[4,5- <i>h</i>][3]benzazepin-3-yl	2	C ₃₃ H ₃₉ N ₃ O.2HCl
289428	OH	1-(4-Pyr)-2,3-dihydro-5-indolyl	3	C ₂₈ H ₃₃ N ₃ O.3HCl
289430	OH	2-(PhCH2)-2,3,4,5-tetrahydro-1 <i>H</i> -2-benzazepin-8-yl	2	C ₃₂ H ₄₀ N ₂ O.2HCl
289431	H	1-(4-Pyr)-2,3-dihydro-5-indolyl	2	C ₂₈ H ₃₃ N ₃ .2HCl

SOURCE – Takeda.

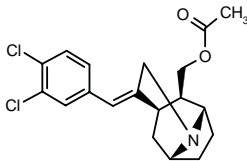
REFERENCES

1. Ishihara, Y. et al. (Takeda Chemical Industries, Ltd.) *Nitrogenous fused heterocycle cpds., process for the preparation thereof and agents containing the same.* WO 0023437.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

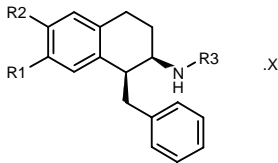
288612

Acetic acid (1*R*,2*R*,3*S*,6*R*,*Z*)-9-(3,4-dichlorophenylmethylidene)-7-azatricyclo[4.3.1.0^{3,7}]decan-2-ylmethyl ester



C19 H21 Cl2 N O2; Mol wt: 366.2859

ACTION – Tricyclic tropane analogue, a potent inhibitor of 5-HT reuptake, as demonstrated in rat midbrain synaptosomes (K_i = 1.6 nM), with high selectivity over noradrenaline and dopamine transporters (K_i = 638 and 1870 nM, respectively). Potentially useful for the treatment of cocaine addiction.



Compound	R1	R2	R3	X	Formula
288681	H	OMe	3,4-(MeO)2-PhCH2CH2	HCl	C ₂₈ H ₃₃ NO ₃ .HCl
288682	H	H	3-indolyl-CH2CH2	fumarate	C ₂₇ H ₂₈ N ₂ .C ₄ H ₄ O ₄
288684	H	H	2-MeO-PhCO	HBr	C ₂₅ H ₂₅ NO ₂ .HBr
288685	OMe	H	3-indolyl-CH2CH2		C ₂₈ H ₃₀ N ₂ O
288686	H	OMe	4-MeO-PhCH2CH2		C ₂₇ H ₃₁ NO ₂

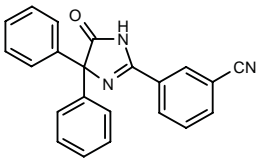
SOURCE – Ortho-McNeil.

REFERENCES

1. Dax, S.L. et al. (Ortho-McNeil Pharmaceutical, Inc.) *N-Aralkylaminotetralins as ligands for the neuropeptide Y Y5 receptor*. WO 0020376.

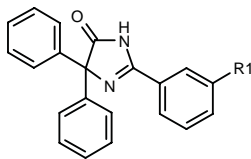
288786

3-(5-Oxo-4,4-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-benzonitrile



C22 H15 N3 O; Mol wt: 337.3805

ACTION – Selective antagonist at neuropeptide Y (NPY) Y₅ receptors that acts as an anorectic and is potentially useful for promoting weight loss in the treatment of obesity and eating disorders. Other exemplified phenyl-substituted imidazolone derivatives include the following:



Compound	R1	Formula
288787	CH2NH2	C ₂₂ H ₁₉ N ₃ O
288788	CH2Cl	C ₂₂ H ₁₇ ClN ₂ O
288790	NO2	C ₂₁ H ₁₅ N ₃ O ₃

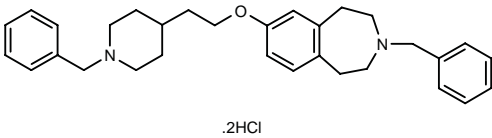
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Poindexter, G.S. et al. (Bristol-Myers Squibb Co.) *Imidazolone anorectic agents: II. Phenyl derivs*. US 6054590.

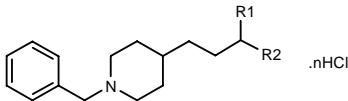
289421

3-Benzyl-7-[2-(1-benzylpiperidin-4-yl)ethoxy]-2,3,4,5-tetrahydro-1*H*-3-benzazepine dihydrochloride



C31 H38 N2 O . 2HCl; Mol wt: 527.5760

ACTION – Antiobesity agent with excellent thermogenesis-stimulating effects, shown to concentration-dependently increase cAMP levels in murine 3T3-L1 cells at 0.001-1 μM. Other compounds from this series of nitrogen-containing fused heterocycles include the following:



Compound	R1	R2	n	Formula
289425	H	7-(PhCH2)-6,7,8,9-tetrahydro-5 <i>H</i> -isoxazolo[4,5- <i>h</i>][3]benzazepin-3-yl	2	C ₃₃ H ₃₉ N ₃ O.2HCl
289428	OH	1-(4-Pyr)-2,3-dihydro-5-indolyl	3	C ₂₈ H ₃₃ N ₃ O.3HCl
289430	OH	2-(PhCH2)-2,3,4,5-tetrahydro-1 <i>H</i> -2-benzazepin-8-yl	2	C ₃₂ H ₄₀ N ₂ O.2HCl
289431	H	1-(4-Pyr)-2,3-dihydro-5-indolyl	2	C ₂₈ H ₃₃ N ₃ .2HCl

SOURCE – Takeda.

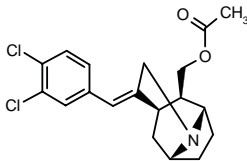
REFERENCES

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TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

288612

Acetic acid (1*R*,2*R*,3*S*,6*R*,*Z*)-9-(3,4-dichlorophenylmethylidene)-7-azatricyclo[4.3.1.0^{3,7}]decan-2-ylmethyl ester



C19 H21 Cl2 N O2; Mol wt: 366.2859

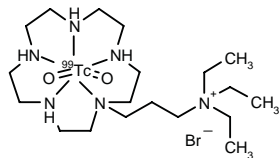
ACTION – Tricyclic tropane analogue, a potent inhibitor of 5-HT reuptake, as demonstrated in rat midbrain synaptosomes (K_i = 1.6 nM), with high selectivity over noradrenaline and dopamine transporters (K_i = 638 and 1870 nM, respectively). Potentially useful for the treatment of cocaine addiction.

NTP-15-5

288323

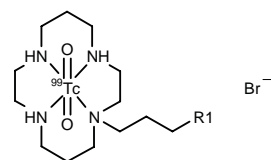
Dioxo[*N,N,N*-Triethyl-3-(1,4,7,10,13-pentaazacyclo-pentadec-1-yl)-1-propanaminium-κ*N*¹,κ*N*⁴,κ*N*⁷, κ*N*¹⁰,κ*N*¹³]technetium(2+)-99Tc monobromide

NTP 15-5



C19 H45 Br N6 O2 Tc; Mol wt: 568.5085

ACTION – Radiodiagnostic agent useful for imaging joints. *In vivo*, compound was shown to rapidly concentrate in articular cartilage and exhibited good stability, being excreted in the urine as the technetium-complexed form. *In vitro* studies conducted on chondrocyte cultures demonstrated that compound is able to bind the acidic functions of proteoglycans. Preclinical scintigraphic studies are currently in progress. The two other quaternary ammonium technetium complexes shown below exhibited *in vivo* instability.



Compound	R1	Formula
NPPC [288321]	1-Pyr	C ₁₈ H ₃₄ BrN ₅ O ₂ Tc
NTPC [288322]	N ⁺ (Et)3	C ₁₉ H ₄₄ BrN ₅ O ₂ Tc

SOURCES – Université Blaise Pascal-Clermont-Ferrand II, Clermont-Ferrand (FR); INSERM, Paris Cedex (FR).

REFERENCES

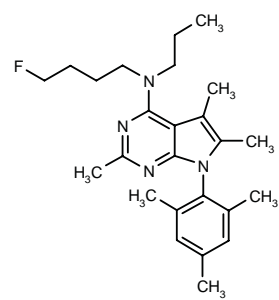
1. Maurizis, J.C. et al. *Disposition in rats of N-pyridinium-propyl-cyclam, N-triethylammoniumpropyl-cyclam, and N-[triethylammonium]-3-propyl-[15]ane-N5, potential cartilage imaging agents.* Drug Metab Dispos 2000, 28(4): 418.

2. Nicolas, C. et al. *Synthesis of N-quaternary ammonium [H-3] and [Tc-99m]polyazamacrocycles, potential radiotracers for cartilage imaging.* J Label Compd Radiopharm 2000, 43(6): 585.

PHARMACOLOGICAL TOOLS

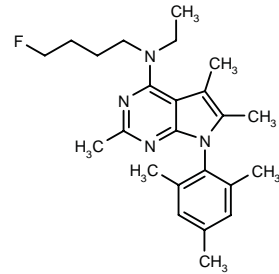
288882

N-(4-Fluorobutyl)-2,5,6-trimethyl-*N*-propyl-7-(2,4,6-trimethylphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



C25 H35 F N4; Mol wt: 410.5775

ACTION – Fluorine-containing antalarmin derivative with high affinity for the corticotropin-releasing factor CRF₁ receptor (K_i = 0.91 nM), potentially useful for the development of [¹⁸F]-containing positron emission tomography (PET) tracers for this receptor for studying the physiological and pathological roles of the CRF system. Another fluorine-containing antalarmin analogue is:



288881: C24 H33 F N4

SOURCE – National Institutes of Health, Bethesda, MD (US).

REFERENCES

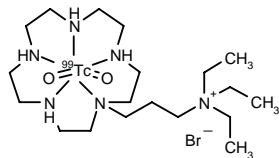
1. Hsin, L.-W. et al. *Synthesis and biological activity of fluoro-substituted pyrrolo[2,3-d]pyrimidines: The development of potential positron emission tomography imaging agents for the corticotropin-releasing hormone type 1 receptor.* Bioorg Med Chem Lett 2000, 10(8): 707.

NTP-15-5

288323

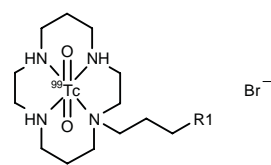
Dioxo[*N,N,N*-Triethyl-3-(1,4,7,10,13-pentaazacyclo-pentadec-1-yl)-1-propanaminium-κ*N*¹,κ*N*⁴,κ*N*⁷, κ*N*¹⁰,κ*N*¹³]technetium(2+)-99Tc monobromide

NTP 15-5



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Compound	R1	Formula
NPPC [288321]	1-Pyr	C ₁₈ H ₃₄ BrN ₅ O ₂ Tc
NTPC [288322]	N ⁺ (Et)3	C ₁₉ H ₄₄ BrN ₅ O ₂ Tc

SOURCES – Université Blaise Pascal-Clermont-Ferrand II, Clermont-Ferrand (FR); INSERM, Paris Cedex (FR).

REFERENCES

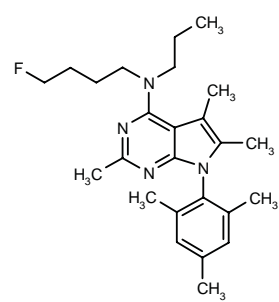
1. Maurizis, J.C. et al. *Disposition in rats of N-pyridinium-propyl-cyclam, N-triethylammoniumpropyl-cyclam, and N-[triethylammonium]-3-propyl-[15]ane-N5, potential cartilage imaging agents.* Drug Metab Dispos 2000, 28(4): 418.

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PHARMACOLOGICAL TOOLS

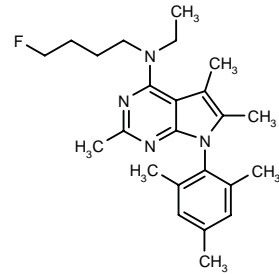
288882

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ACTION – Fluorine-containing antalarmin derivative with high affinity for the corticotropin-releasing factor CRF₁ receptor (K_i = 0.91 nM), potentially useful for the development of [¹⁸F]-containing positron emission tomography (PET) tracers for this receptor for studying the physiological and pathological roles of the CRF system. Another fluorine-containing antalarmin analogue is:



288881: C24 H33 F N4

SOURCE – National Institutes of Health, Bethesda, MD (US).

REFERENCES

1. Hsin, L.-W. et al. *Synthesis and biological activity of fluoro-substituted pyrrolo[2,3-d]-pyrimidines: The development of potential positron emission tomography imaging agents for the corticotropin-releasing hormone type 1 receptor.* Bioorg Med Chem Lett 2000, 10(8): 707.

TIF-B1

289066

Tumor necrosis factor-inhibitory protein with a molecular weight of about 27 kD

TIP-B1

ACTION – Protein with TNF-inhibitory activity and potential in the treatment of TNF-mediated diseases. As demonstrated in different assays, this protein is able to inhibit the actions of TNF upon a cell, such as TNF-induced cell lysis and apoptosis, when introduced into the extracellular medium surrounding the cell, while being free of sequences which interfere with normal cellular TNF binding sites and of sequences which directly bind to TNF.

SOURCE – Health Research.

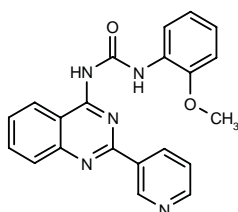
REFERENCES

1. Berleth, E. et al. (Health Research, Inc.) *Tumor necrosis factor inhibitory protein TIP-B1 and method of using same*. EP 0997475.

VUF-5574

289145

N-(2-Methoxyphenyl)-*N'*-[2-(3-pyridinyl)quinazolin-4-yl]urea



C21 H17 N5 O2; Mol wt: 371.3983

M.p. 257-8 °C.

ACTION – Potent and selective adenosine A₃ receptor antagonist, a quinazoline urea analogue that exhibits high affinity for adenosine A₃ receptors ($K_i = 4$ nM) and at least 2,500-fold selectivity versus A₁ and A_{2A} receptors. In an *in vitro* functional assay, compound competitively antagonized the inhibition of cAMP production induced by the adenosine agonist NECA in CHO cells expressing human A₃ receptors with a pA₂ value of 8.1. Potentially useful as a tool for the pharmacological characterization of the human A₃ receptor.

SOURCE – Vrije Universiteit, Amsterdam (NL).

REFERENCES

1. van Muijlwijk-Koezen, J.E. et al. *Isoquinoline and quinazoline urea analogues as antagonists for the human adenosine A₃ receptor*. J Med Chem 2000, 43(11): 2227.

ZFSTA

289346

Follistatin-related protein with a predicted molecular weight of about 86 kD

ACTION – Human protein from the follistatin family, which is believed to play a major role in regulating the biological activities of TGF- β growth factors, and in particular may play a broad role in development and differentiation, atherosclerosis pathogenesis, regulation of the gonadal-pituitary-hypothalamic axis, tooth and bone formation, regulation of gonadal hormone production, spermatogenesis, hypothalamic oxytocin secretion, proliferation and differentiation of erythroid progenitors, hematopoiesis, host defense and neuron survival. Also disclosed are polynucleotides encoding this protein and antibodies to the protein.

SOURCE – ZymoGenetics.

REFERENCES

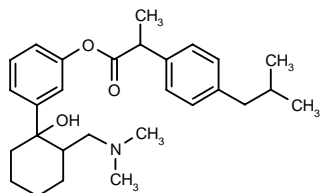
1. Conklin, D.C. and Ellsworth, J.L. (ZymoGenetics, Inc.) *Follistatin-related protein zfstaz2*. WO 0022126.

ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

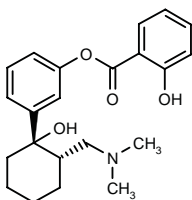
290134

2-(4-Isobutylphenyl)propionic acid 3-[2-(dimethylamino-methyl)-1-hydroxycyclohexyl]phenyl ester



C₂₈ H₃₉ N O₃; Mol wt: 437.6201

ACTION – Analgesic agent with improved activity, reduced toxicity and a longer duration of action compared to tramadol. When tested in the rat hot-plate test, compound increased response time by $210 \pm 88\%$ at 20 $\mu\text{mol/kg}$ p.o. compared to $87 \pm 23\%$ for tramadol at the same dose, with a longer duration of action. LD₅₀ = 900 mg/kg p.o. in mice vs. 350 mg/kg p.o. for tramadol. Another exemplified compound from this series of esters of *O*-desmethyltramadol is:



290136: C₂₂ H₂₇ N O₄

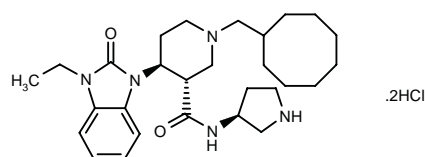
SOURCE – Vita.

REFERENCES

1. Del Castillo Nieto, J.C. et al. (Laboratorios Vita, SA) *New esters derived from subst. phenyl-cyclohexyl cpds.* WO 0027799.

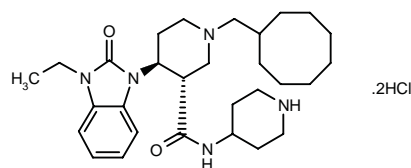
290582

(3*S**,4*S**)-1-(Cyclooctylmethyl)-4-(3-ethyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-*N*-[pyrrolidin-3(*S*)-yl]piperidine-3-carboxamide dihydrochloride



C₂₈ H₄₃ N₅ O₂ . 2HCl; Mol wt: 554.6025

ACTION – Opioid receptor-like (ORL1, nociceptin, N/OFQ) receptor antagonist (IC₅₀ = 5.2 nM against [¹²⁵I]-Tyr¹⁴-nociceptin binding in CHO cells expressing the human receptor) with potential in the treatment of a broad range of conditions such as pain, obesity, cognition impairment, schizophrenia, Parkinson's disease, depression, diabetes, polyuria and hypotension. Another compound from this series of 2-oxoimidazole derivatives is:



290583: C₂₉ H₄₅ N₅ O₂ . 2HCl

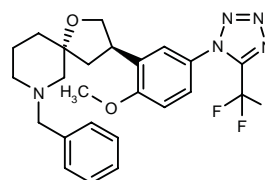
SOURCE – Banyu.

REFERENCES

1. Kawamoto, H. et al. (Banyu Pharmaceutical Co., Ltd.) *2-Oxoimidazole derivs.* WO 0031061.

290723

(±)-*trans*-7-Benzyl-3-[2-methoxy-5-[5-(trifluoromethyl)-1*H*-tetrazol-1-yl]phenyl]-1-oxa-7-azaspiro[4.5]decane



C₂₄ H₂₆ F₃ N₅ O₂; Mol wt: 473.4964

ACTION – Tachykinin NK₁ receptor antagonist (IC₅₀ = 0.4 nM using human receptors) potentially useful in the treatment of pain, inflammation, migraine, emesis and postherpetic neuralgia.

SOURCE – Merck & Co.

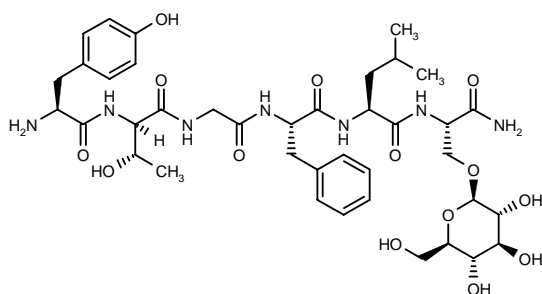
REFERENCES

1. Curtis, N.R. et al. (Merck Sharp & Dohme Ltd.) *Spiro-piperidine derivs. and their use as therapeutic agents*. EP 0912579, US 6071928, WO 9801450.

2. Curtis, N.R. et al. *Synthesis and SAR of a novel series of 3-aryl-7-alkyl-1-oxa-7-azaspiro[4.5]decane NK1 receptor antagonists*. 27th Natl Med Chem Symp (June 13-17, Kansas City) 2000, Abst A-06.

291173

L-Tyrosyl-D-threonyl-glycyl-L-phenylalanyl-L-leucyl-O-(β-D-glucopyranosyl)-L-serinamide



C39 H57 N7 O14; Mol wt: 847.9143

ACTION – Enkephalin glycopeptide analogue with nanomolar affinity for delta (DOP) and mu opioid (MOP) receptors (IC₅₀ = 8.2 and 3.4 nM, respectively) and functional agonist activity at both DOP and MOP receptors (IC₅₀ = 1.6 and 33.8 nM in mouse vas deferens and guinea pig ileum, respectively). Compound penetrates the blood-brain barrier and exhibits analgesic activity in the tail-flick test in mice after i.c.v. administration (ED₅₀ = 0.02 nmol/kg), as well as after i.v., i.p. and s.c. administration (ED₅₀ = 11.4, 34.3 and 7.2 mmol/kg, respectively), with potency comparable to morphine. In addition, it produced less physical dependence in mice than equivalent doses of morphine using an acute model. Potentially useful for the treatment of chronic pain.

SOURCES – University of Arizona, Tucson, AZ (US); University of Northern Colorado, Greeley, CO (US).

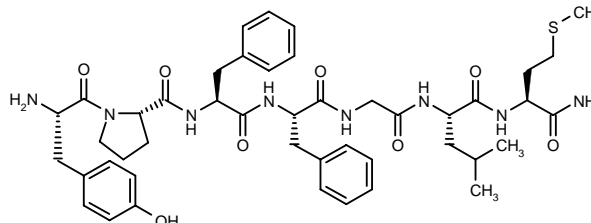
REFERENCES

1. Bilsky, E.J. et al. *Enkephalin glycopeptide analogues produce analgesis with reduced dependence liability*. J Med Chem 2000, 43(13): 2586.

ESP-7

290068

L-Tyrosyl-L-prolyl-L-phenylalanyl-L-phenylalanyl-glycyl-L-leucyl-L-methioninamide



C45 H60 N8 O8 S; Mol wt: 873.0830

ACTION – Analgesic agent, a chimeric peptide containing overlapping NH₂- and COOH-terminal functional domains of the endogenous opioid endomorphin-2 (EM-2) and the tachykinin substance P, respectively. Compound showed moderate affinity for both mu opioid and tachykinin NK₁ receptors (K_i = 218 and 289 nM, respectively) and exhibited *in vitro* functional agonism of substance P-mediated stimulation of inositol phosphate turnover (EC₅₀ = 27 nM) and of mu opioid receptor-mediated inhibition of cAMP production (IC₅₀ = 94.8 nM). When administered into rat spinal cord once daily at doses of 0.05, 0.2 and 1 μg, it induced opioid-dependent analgesia without loss of potency over 5 days. Potentially useful for the treatment of acute and chronic pain.

SOURCES – Polish Academy of Science, Kraków (PL); Tufts University School of Medicine, Boston, MA (US).

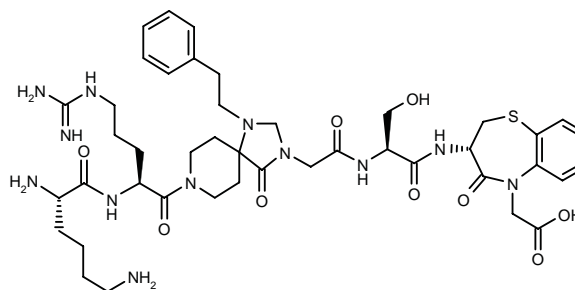
REFERENCES

1. Foran, S.E. et al. *A substance P-opioid chimeric peptide as a unique nontolerance-forming analgesic*. Proc Natl Acad Sci USA 2000, 97(13): 7621.

JMV-1640

290154

3(S)-[1'-(L-Lysyl-L-arginyl)-3-(2-phenylethyl)-5-oxo-spiro[imidazolidin-4,4'-piperidin]-1-yl]acetyl-L-serylamine-4-oxo-3,4-dihydro-2H-1,5-benzothiazepine-5-acetic acid



C43 H62 N12 O9 S; Mol wt: 923.1038

ACTION – Bradykinin B₁ receptor antagonist with high affinity ($K_i = 24.10$ nM against human cloned receptors expressed in 293 cells) and no affinity for bradykinin B₂ receptors. Functional studies on human umbilical vein preparations showed that compound competitively antagonized contractions induced by the potent B₁ receptor agonist [des-Arg¹⁰]-kallidin ($pA_2 = 6.1$). Considered a lead compound for the further design of potent nonpeptide bradykinin B₁ receptor antagonists useful for the treatment of inflammatory pain.

SOURCES – Fournier; INSERM, Paris Cedex (FR); Université Montpellier I, Montpellier (FR); Université Montpellier II, Montpellier (FR).

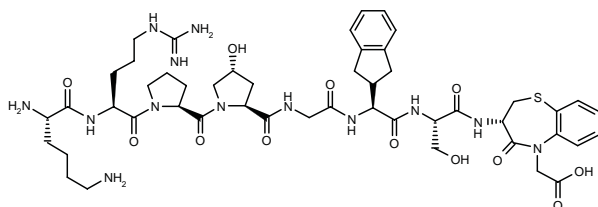
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1. Bedos, P. et al. A rational approach to the design and synthesis of a new bradykinin B₁ receptor antagonist. *J Med Chem* 2000, 43(12): 2387.

JMV-1645

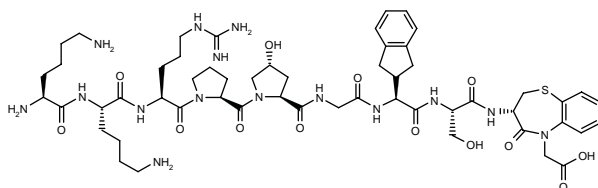
289468

3(S)-[L-Lysyl-L-arginyl-L-prolyl-L-(*trans*-4-hydroxy)prolyl-glycyl-L-[α -(2-indanyl)]glycyl-L-serylamino]-4-oxo-3,4-dihydro-2H-1,5-benzothiazepine-5-acetic acid



C49 H69 N13 O12 S; Mol wt: 1064.2290

ACTION – Bradykinin B₁ receptor antagonist with high affinity for B₁ receptors ($K_i = 0.023$ nM) and selectivity over B₂ receptors ($K_i = 9.2$ nM). Compound exhibited potent antagonist activity at B₁ receptors ($pA_2 = 8.0$) in isolated human umbilical vein. Potentially useful for the treatment of pain associated with chronic inflammatory conditions. Another des-Arg analogue of the potent B₂ antagonist JMV-1116 is:



JMV-1639 [289470]: C55 H81 N15 O13 S

SOURCES – CNRS; Fournier; Université Montpellier I, Montpellier (FR); Université Montpellier II, Montpellier (FR).

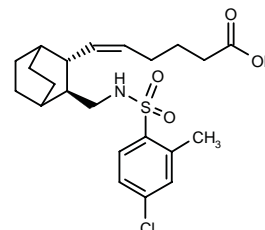
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ONO-8711*2-10

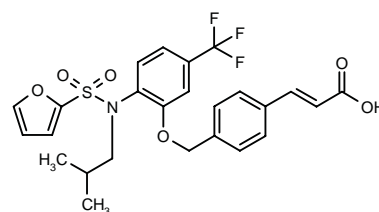
270563

6-[(2*R*,3*S*)-3-(4-Chloro-2-methylphenylsulfonamido-methyl)bicyclo[2.2.2]oct-2-yl]-5(*Z*)-hexenoic acid



C22 H30 Cl N O4 S; Mol wt: 440.0010

ACTION – Potent, orally active prostanoid EP₁ receptor antagonist with high affinity for EP₁ receptors ($K_i = 1.7$ nM), as well as for the TP receptor ($K_i = 7.6$ nM), and functional antagonist activity. *In vivo*, compound (given i.d.) was able to inhibit the increase in micturition pressure induced by an EP₁ agonist in anesthetized rats, to decrease the late-phase formalin response in rats in a dose-dependent fashion after oral administration, as well as to reduce tactile allodynia induced by intrathecal administration of PGE₂ in rats. Ono-8711 was also found to significantly reduce the number and the volume of mammary gland tumors in a carcinogenesis model in rats and of colon carcinoma induced by azoxymethane in knockout mice deficient in EP₁ and EP₂ receptors. Potentially useful as an analgesic and as a chemo-preventive against mammary and colon cancers. Another, more selective EP₁ receptor antagonist is:



ONO-8713 [268237],1,4,5,7:** C25 H24 F3 N O6 S

SOURCE – Ono.

REFERENCES

1. Ohuchida, S. and Nagao, Y. (Ono Pharmaceutical Co., Ltd.) Sulfonamide and carboxamide derivs. and drugs containing the same as the active ingredient. EP 0947500, WO 9827053.
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3. Kawamori, T. et al. Inhibitory effects of a selective prostaglandin E receptor subtype EP₁ antagonist, ONO-8711, on PhIP-induced mammary carcinogenesis. *Proc Amer Assoc Cancer Res* 2000, 41: Abst 3657.
4. Maruyama, T. et al. Novel selective EP₁ receptor antagonists inhibit allodynia in rats. 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 50.
5. Maruyama, T. et al. Novel two types of orally active AP₁ receptor antagonists. *Prostaglandins Other Lipid Mediat* 1999, 59(1-6): Abst 216.
6. Miura, A. et al. Effect of EP₁ antagonist (ONO8711) on preganglionic neurons in neonatal rat lumbosacral parasympathetic nucleus. *Soc Neurosci Abst* 1999, 25(Part 1): Abst 473.6.
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10. Ono Pharmaceutical Product Pipeline 1999, May.

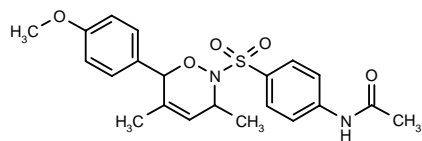
*Identified compound **270563** (see **270562**) *Drug Data Rep* 1999, 021(01): 0016.

Identified compound **268237 (see **268235**) *Drug Data Rep* 1998, 020(10): 0870.

ANTIMIGRAINE DRUGS

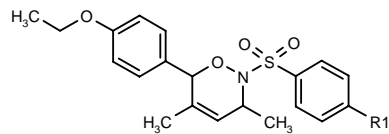
289715

N-[4-[6-(4-Methoxyphenyl)-3,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazin-2-ylsulfonyl]phenyl]acetamide



C21 H24 N2 O5 S; Mol wt: 416.4956

ACTION – Selective metabotropic glutamate mglu₁ receptor antagonist for the treatment of CNS disorders such as cognition disorders and neurodegenerative diseases, and specifically claimed for the treatment of migraine and pain associated therewith. Other compounds from this series of *N*-substituted-3,6-dihydro-2*H*-1,2-oxazine derivatives are:



Compound	R1	Formula
289716	NHAc	C ₂₂ H ₂₆ N ₂ O ₅ S
289717	CONHMe	C ₂₂ H ₂₆ N ₂ O ₅ S

SOURCE – Lilly.

REFERENCES

1. Clark, B.P. et al. (Eli Lilly and Company, Ltd.) *N*-Substd. (3,6-dihydro)-2*H*-1,2-oxazine derivs., their preparation and their use as selective mGluR1 antagonists. WO 0026198.

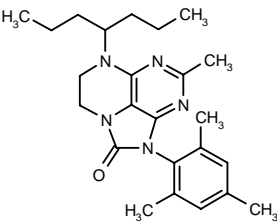
2. Clark, B.P. et al. (Eli Lilly and Company, Ltd.) *Pharmaceutical cpds*. WO 0026199.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

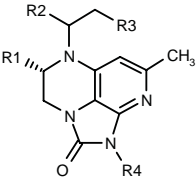
289922

2-Methyl-9-(1-propylbutyl)-4-(2,4,6-trimethylphenyl)-5,7,8,9-tetrahydro-4*H*-imidazo[4,5,1-*de*]pteridin-5-one



C24 H33 N5 O; Mol wt: 407.5587

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist (K_i < 250 nM) with potential in the treatment of disorders characterized by CRF hypersecretion such as stroke, anxiety, depression, panic, obsessive–compulsive disorder, unstable angina, hypertension, anorexia, bulimia, substance abuse, irritable bowel syndrome, inflammation and epilepsy. Other tricyclic compounds include the following:



Compound	R1	R2	R3	R4	Formula
289923	H	Pr	Et	2,4,6-(F)3-Ph	C ₂₂ H ₂₅ F ₃ N ₄ O
289924	H	Pr	Et	1,4-benzodioxan-6-yl	C ₂₄ H ₃₀ N ₄ O ₃
289925	H	Pr	Pr	4-Cl-2-Me-Ph	C ₂₄ H ₃₁ ClN ₄ O
289926	H	Pr	Et	4-MeO-3-Pyr	C ₂₂ H ₂₉ N ₅ O ₂
289927	Et	H	OH	4-MeO-Ph	C ₂₀ H ₂₄ N ₄ O ₃

SOURCE – Neurocrine Biosciences.

REFERENCES

1. Haddach, M. et al. (Neurocrine Biosciences Inc.) *CRF receptor antagonists and methods relating thereto*. WO 0027850.

8. Watanabe, K. et al. *Role of the prostaglandin E receptor subtype EP1 in colon carcinogenesis*. *Cancer Res* 1999, 59(20): 5093.

9. *1999 annual report reflects progress in clinical trials at Ono*. *DailyDrugNews.com* (Daily Essentials) 1999, Oct 28.

10. Ono Pharmaceutical Product Pipeline 1999, May.

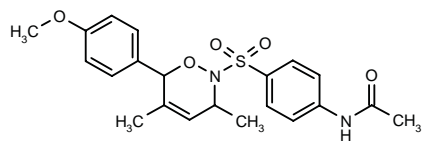
*Identified compound **270563** (see **270562**) *Drug Data Rep* 1999, 021(01): 0016.

Identified compound **268237 (see **268235**) *Drug Data Rep* 1998, 020(10): 0870.

ANTIMIGRAINE DRUGS

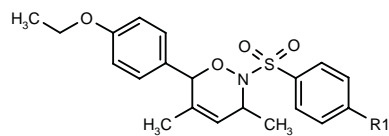
289715

N-[4-[6-(4-Methoxyphenyl)-3,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazin-2-ylsulfonyl]phenyl]acetamide



C21 H24 N2 O5 S; Mol wt: 416.4956

ACTION – Selective metabotropic glutamate mglu₁ receptor antagonist for the treatment of CNS disorders such as cognition disorders and neurodegenerative diseases, and specifically claimed for the treatment of migraine and pain associated therewith. Other compounds from this series of *N*-substituted-3,6-dihydro-2*H*-1,2-oxazine derivatives are:



Compound	R1	Formula
289716	NHAc	C ₂₂ H ₂₆ N ₂ O ₅ S
289717	CONHMe	C ₂₂ H ₂₆ N ₂ O ₅ S

SOURCE – Lilly.

REFERENCES

1. Clark, B.P. et al. (Eli Lilly and Company, Ltd.) *N*-Substd. (3,6-dihydro)-2*H*-1,2-oxazine derivs., their preparation and their use as selective mGluR1 antagonists. WO 0026198.

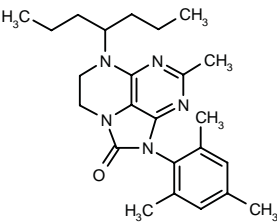
2. Clark, B.P. et al. (Eli Lilly and Company, Ltd.) *Pharmaceutical cpds*. WO 0026199.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

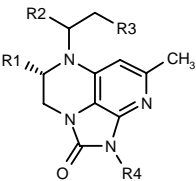
289922

2-Methyl-9-(1-propylbutyl)-4-(2,4,6-trimethylphenyl)-5,7,8,9-tetrahydro-4*H*-imidazo[4,5,1-*de*]pteridin-5-one



C24 H33 N5 O; Mol wt: 407.5587

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist (K_i < 250 nM) with potential in the treatment of disorders characterized by CRF hypersecretion such as stroke, anxiety, depression, panic, obsessive–compulsive disorder, unstable angina, hypertension, anorexia, bulimia, substance abuse, irritable bowel syndrome, inflammation and epilepsy. Other tricyclic compounds include the following:



Compound	R1	R2	R3	R4	Formula
289923	H	Pr	Et	2,4,6-(F)3-Ph	C ₂₂ H ₂₅ F ₃ N ₄ O
289924	H	Pr	Et	1,4-benzodioxan-6-yl	C ₂₄ H ₃₀ N ₄ O ₃
289925	H	Pr	Pr	4-Cl-2-Me-Ph	C ₂₄ H ₃₁ ClN ₄ O
289926	H	Pr	Et	4-MeO-3-Pyr	C ₂₂ H ₂₉ N ₅ O ₂
289927	Et	H	OH	4-MeO-Ph	C ₂₀ H ₂₄ N ₄ O ₃

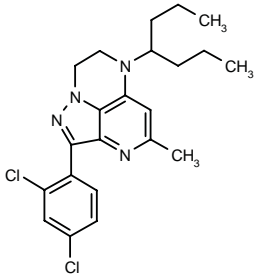
SOURCE – Neurocrine Biosciences.

REFERENCES

1. Haddach, M. et al. (Neurocrine Biosciences Inc.) *CRF receptor antagonists and methods relating thereto*. WO 0027850.

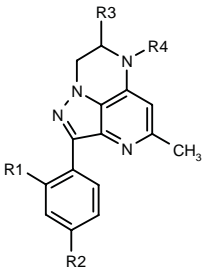
290071

2-(2,4-Dichlorophenyl)-4-methyl-6-(1-propylbutyl)-7,8-dihydro-6*H*-1,3,6,8a-tetraazaacenaphthylene



C22 H26 Cl2 N4; Mol wt: 417.3814

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist ($K_i < 250$ nM) for the treatment of disorders related to the hypersecretion of CRF, particularly stroke, depression and anxiety. Other exemplified tricyclic compounds include the following:



Compound	R1	R2	R3	R4	Formula
290072	Cl	Cl	Pr	Pr	C ₂₁ H ₂₄ Cl ₂ N ₄
290073	Cl	Me	(S)-Et	cyclopropyl-CH ₂	C ₂₂ H ₂₅ ClN ₄
290074	CF ₃	Cl	(S)-Et	CH ₂ CH ₂ OMe	C ₂₁ H ₂₂ ClF ₃ N ₄ O
290075	Me	OMe	H	CH(Bu) ₂	C ₂₆ H ₃₆ N ₄ O
290076	OMe	CF ₃	Et	CH ₂ CH ₂ NHAc	C ₂₃ H ₂₆ F ₃ N ₅ O ₂
290077	OMe	CF ₃	Et	CH ₂ CH(OH)CH ₂ CH ₂ OBu	C ₂₇ H ₃₅ F ₃ N ₄ O ₃
290078	OMe	CF ₃	(S)-Et	cyclopropyl-CH ₂ N(Pr)CH ₂ CH ₂	C ₂₈ H ₃₆ F ₃ N ₅ O
290079	OMe	CF ₃	Et	i-PrNHCO	C ₂₃ H ₂₆ F ₃ N ₅ O ₂

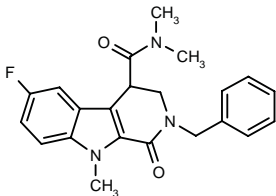
SOURCE – Neurocrine Biosciences.

REFERENCES

1. Haddach, M. et al. (Neurocrine Biosciences Inc.) *CRF receptor antagonists and methods relating thereto*. WO 0027846.

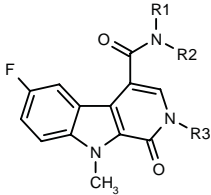
290444

(±)-2-Benzyl-6-fluoro-*N,N*,9-trimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carboxamide

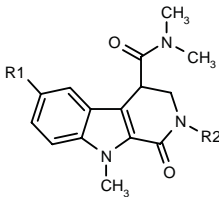


C22 H22 F N3 O2; Mol wt: 379.4328

ACTION – Full or partial agonist at ω_1 (type 1) and ω_2 (type 2) benzodiazepine sites on GABA_A receptors with anxiolytic, hypnotic and anticonvulsant properties. The compound may also be useful for the treatment of other disorders associated with GABAergic transmission. A representative compound from a series of 1*H*-pyrido[3,4-*b*]indole-4-carboxamide derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
290445	Me	Me	CH ₂ Ph	C ₂₂ H ₂₀ FN ₃ O ₂
290449	Me	Me	Ph	C ₂₁ H ₁₈ FN ₃ O ₂
290451	Me	Et	Ph	C ₂₂ H ₂₀ FN ₃ O ₂
290452	-(CH ₂) ₄ -		Ph	C ₂₃ H ₂₀ FN ₃ O ₂
290453	Me	Me	2-Pyr	C ₂₀ H ₁₇ FN ₄ O ₂
290454	-(CH ₂) ₄ -		5-Me-1,3,4-thiadiazol-2-yl	C ₂₀ H ₁₈ FN ₅ O ₂ S



Compound	R1	R2	Isomer	Formula
290446	Cl	CH ₂ CH ₂ OMe		C ₁₈ H ₂₂ ClN ₃ O ₃
290447	F	CH ₂ Ph	+	C ₂₂ H ₂₂ FN ₃ O ₂
290448	F	CH ₂ Ph	-	C ₂₂ H ₂₂ FN ₃ O ₂
290450	H	Ph		C ₂₁ H ₂₁ N ₃ O ₂

SOURCE – Sanofi-Synthélabo.

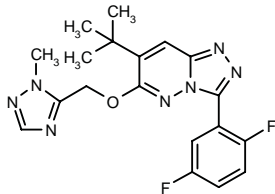
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L-838417

290487

7-*tert*-Butyl-3-(2,5-difluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-5-ylmethoxy)[1,2,4]triazolo[4,3-*b*]pyridazine



C19 H19 F2 N7 O; Mol wt: 399.4031

ACTION – Anxiolytic agent that acts at the benzodiazepine site of the GABA_A receptor as a functionally selective allosteric agonist at $\alpha 2$, $\alpha 3$ and $\alpha 5$ subtypes, and as an antagonist at the $\alpha 1$ subtypes. Compound displays nanomolar affinity for the benzodiazepine site of GABA_A receptors in murine brain preparations ($K_i = 1.24$ nM) and for $\alpha 1\beta 3\gamma 2$, $\alpha 2\beta 3\gamma 2$, $\alpha 3\beta 3\gamma 2$ and $\alpha 5\beta 3\gamma 2$ subtypes ($K_i = 0.67$ - 2.25 nM), but significantly reduced affinity for $\alpha 4\beta 3\gamma 2$ and $\alpha 6\beta 3\gamma 2$ subtypes ($K_i > 1$ μ M). Furthermore, it demonstrated partial agonist activity at the $\alpha 2$, $\alpha 3$ and $\alpha 5$ subtypes, and antagonist activity at the $\alpha 1$ subtype. *In vivo*, compound given orally was found to retain anxiolytic activity in the plus maze and in the fear-potentiated startle paradigm in rats, and anticonvulsant activity against chemically (pentylenetetrazol) induced seizures in mice, as well as audiogenic seizures. Unlike diazepam, it did not impair rotarod performance in wild-type or genetically modified mice with a diazepam-insensitive GABA_A receptor $\alpha 1$ subtype ($\alpha 1$ H101R), and it produced an initial stimulation of locomotor activity in a novel environment in both types of mice. Furthermore, in the chain-pulling test of sedation in rats, compound had no effect at doses almost completely occupying benzodiazepine-sensitive binding sites, whereas diazepam significantly impaired performance.

SOURCE – Merck Sharp & Dohme.

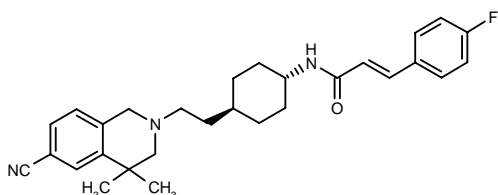
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2. Carling, W.R. et al. (Merck Sharp & Dohme Ltd.) *Triazolo-pyridazine derivs. as ligands for GABA receptors*. WO 0044752.
3. McKernan, R.M. et al. *Sedative but not anxiolytic properties of benzodiazepines are mediated by the GABA_A receptor α_1 subtype*. Nat Neurosci 200, 3(6): 587.

ANTIPSYCHOTIC DRUGS

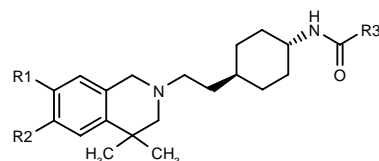
289609

trans-N-[4-[2-(6-Cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-3-(4-fluorophenyl)-2(*E*)-propenamide



C29 H34 F N3 O; Mol wt: 459.6056

ACTION – Antipsychotic agent with selective affinity for dopamine D3 receptors; it was reported to have pK_i values of 7.0-8.0 in binding experiments using cloned human D3 receptors. Other specifically claimed tetrahydroisoquinoline derivatives are:



Compound	R1	R2	R3	Formula
289610	H	CN	4-quinolyl	C ₃₀ H ₃₄ N ₄ O
289611	CN	H	(<i>E</i>)-4-F-PhCH=CH	C ₂₉ H ₃₄ FN ₃ O
289612	H	H	(<i>E</i>)-4-F-PhCH=CH	C ₂₈ H ₃₆ FN ₂ O
289613	H	H	3-indolyl-CH ₂	C ₂₉ H ₃₇ N ₃ O
289615	H	H	2-indolyl	C ₂₈ H ₃₅ N ₃ O
289616	H	H	1H-pyrrolo[2,3-b]pyridin-3-yl	C ₂₇ H ₃₄ N ₄ O

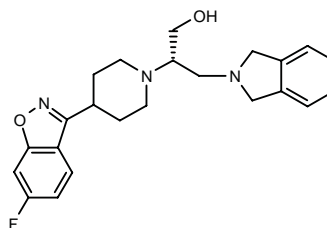
SOURCE – SmithKline Beecham.

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1. Johnson, C.N. and Stemp, G. (SmithKline Beecham plc) *Compounds*. WO 0024717.

290716

(*S*)-3-(1,3-Dihydro-2*H*-isoindol-2-yl)-2-[4-(6-fluorobenzisoxazol-3-yl)piperidin-1-yl]propan-1-ol



C23 H26 F N3 O2; Mol wt: 395.4754

ACTION – Potent dopamine D4 receptor antagonist with good selectivity over dopamine D2 receptors and α_1 -adrenoceptors.

SOURCES – Aventis Pharma; NPS Allelix.

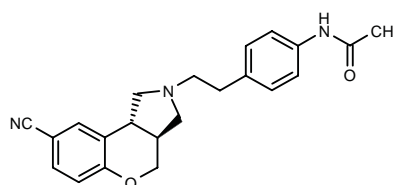
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2. Hendrix, J.A. et al. *Synthesis and SAR of isoindoliny benzisoxazolpiperidines as potent and selective human dopamine D4 receptor antagonists*. 27th Natl Med Chem Symp (June 13-17, Kansas City) 2000, Abst B-07.

S-33138*

271411

N-[4-[2-[(3*aS*,9*bR*)-8-Cyano-1,2,3,3*a*,4,9*b*-hexahydro-[1]benzopyrano[3,4-*c*]pyrrol-2-yl]ethyl]phenyl]acetamide



C22 H23 N3 O2; Mol wt: 361.4427

ACTION – Potent and selective dopamine D3 antagonist with 15-fold higher affinity for the D3 over the D2 receptor ($K_i = 2.8$ and 45 nM, respectively) and higher functional antagonist activity at human D3 versus human D2 receptors ($K_b = 1.5$ and 17 nM, respectively, against [35 S]-GTP γ S binding). *In vivo*, at a dose of 2.5 mg/kg s.c. it abolished the effects of the preferential D3 agonist PD-128907 including inhibition of dopamine release in the frontal cortex of freely moving rats and hypothermia. Compound exhibited antipsychotic activity in behavioral models in rats such as inhibition of amphetamine- or phencyclidine-induced locomotion and inhibition of DOI-induced head twitches ($ED_{50} = 1.9, 0.6$ and 1.2 mg/kg s.c., respectively), while showing a relative absence of extrapyramidal symptoms ($ED_{50} = 19.3$ mg/kg s.c. for induction of catalepsy). In addition, it is able to enhance active social interaction in rats, a model pertinent to negative symptomatology ($MED = 0.16$ mg/kg s.c.). In comparison to raclopride, a nonselective D2/D3 antagonist, compound exhibited a more pronounced separation of antipsychotic and extrapyramidal effects.

SOURCE – Servier.

REFERENCES

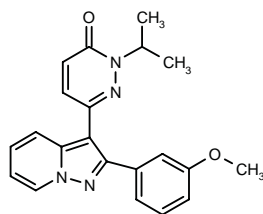
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2. Dubuffet, T. et al. *Novel benzopyrano[3,4-c]pyrrole derivatives as potent and selective dopamine D3 receptor antagonists*. Bioorg Med Chem Lett 1999, 9(14): 2059.
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*Identified compound **271411** Drug Data Rep 1999, 021(02): 0115.

TREATMENT OF MOOD DISORDERS

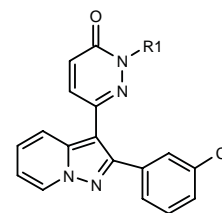
289523

2-Isopropyl-6-[2-(3-methoxyphenyl)pyrazolo[1,5-a]pyridin-3-yl]pyridazin-3(2H)-one



C₂₁ H₂₀ N₄ O₂; Mol wt: 360.4150

ACTION – Adenosine antagonist with dual activity at adenosine A₁ and A₂, particularly A_{2A}, receptors ($K_i = 1$ and 1.7 nM when tested for human adenosine A₁ and A_{2A} receptor binding, respectively). The compound is expected to be useful for the treatment or prevention of depression, dementia, Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure and the like. Other exemplified pyrazolopyridine derivatives are:



Compound	R1	Formula
289524	H	C ₁₇ H ₁₁ ClN ₄ O
289526	Me	C ₁₈ H ₁₃ ClN ₄ O

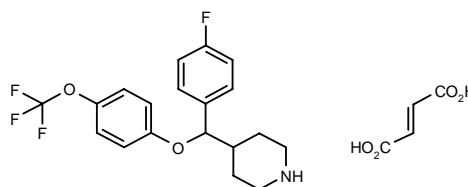
SOURCE – Fujisawa.

REFERENCES

1. Akahane, A. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Pyrazolopyridine as adenosine antagonists*. WO 0024742.

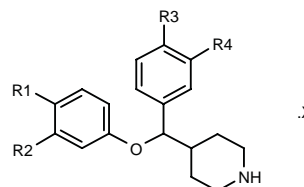
290025

(±)-4-[1-(4-Fluorophenyl)-1-[4-(trifluoromethoxy)phenoxy]-methyl]piperidine fumarate



C₁₉ H₁₉ F₄ N O₂ . C₄ H₄ O₄; Mol wt: 485.4277

ACTION – Antidepressant, a potent inhibitor of 5-HT and/or noradrenaline reuptake. It is also potentially useful for the treatment of bulimia nervosa, obsessive-compulsive disorders, alcohol addiction, anxiety, panic, pain, premenstrual syndrome, social phobia and migraine. Other exemplified 4-substituted-piperidine derivatives are:



Compound	R1	R2	R3	R4	Isomer	X	Formula
290027	F	H	F	H	racemic	HCl	C ₁₈ H ₁₉ F ₂ NO.HCl
290029	F	H	H	H	racemic	H ₂ SO ₄	C ₁₈ H ₂₀ FNO.H ₂ O ₄ S
290030	H	F	H	H	racemic	H ₂ SO ₄	C ₁₈ H ₂₀ FNO.H ₂ O ₄ S
290031	H	F	H	H	(-)		C ₁₈ H ₂₀ FNO
290032	F	H	H	H	(+)		C ₁₈ H ₂₀ FNO
290033	F	H	H	H	(-)		C ₁₈ H ₂₀ FNO
290034	H	F	H	F	racemic	H ₂ SO ₄	C ₁₈ H ₁₉ F ₂ NO.H ₂ O ₄ S

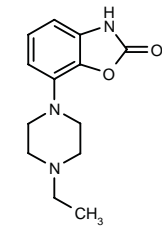
SOURCE – FAES.

REFERENCES

1. FAES. *4-[(Aryl)(aryloxy)methyl]piperidine derivs. and their use as serotonin and/or noradrenaline reuptake inhibitors*. EP 1002794, JP 2000154176.

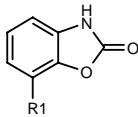
290287

7-(4-Ethylpiperazin-1-yl)benzoxazol-2(3H)-one



C13 H17 N3 O2; Mol wt: 247.2963

ACTION – Dual partial agonist at dopamine D2 and 5-HT_{1A} receptors reported to exhibit high efficacy in the conditioned ultrasonic vocalization model in rats and to be active in models predictive of antidepressant activity. Based on this profile, the compound is considered to be useful for the treatment of dopaminergic and/or serotonergic disorders, particularly anxiety and depression. Other exemplified compounds from this series of piperazine and piperidine derivatives are:



Compound	R1	Formula
290288	4-Me-1-Piz	C ₁₂ H ₁₅ N ₃ O ₂
290289	1-Me-1,2,3,6-tetrahydro-4-Pyr	C ₁₃ H ₁₄ N ₂ O ₂

SOURCE – Duphar.

REFERENCES

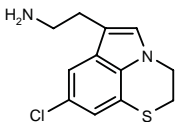
1. Toorop, G.P. et al. (Duphar International Research BV) *New piperazine and piperidine cpds.* WO 0029397.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

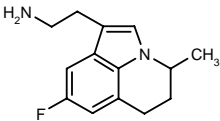
290181

2-(8-Chloro-2,3-dihydropyrrolo[1,2,3-*de*]-1,4-benzothiazin-6-yl)-1-ethanamine



C12 H13 Cl N2 S; Mol wt: 252.7677

ACTION – Potent 5-HT_{2C} receptor agonist (EC₅₀ = 0.23 nM for intracellular calcium mobilization in HEK-293 cells expressing human 5-HT_{2C} receptors) with very good functional selectivity over 5-HT_{2A} receptors (EC₅₀ = 348 nM); compound exhibited moderate affinity for the 5-HT_{2C} receptor expressed in HEK-293 cells (K_i = 47 nM) and good binding selectivity over the 5-HT_{2A} subtype (K_i = 631 nM). Potentially useful for the treatment of epilepsy and obesity. Another compound within this series of pyrrolo[3,2,1-*ij*]quinoline derivatives is:



290180: C14 H17 F N2

SOURCE – NPS Allelix.

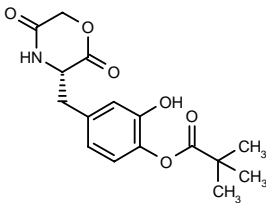
REFERENCES

1. Isaac, M. et al. *Pyrrolo[3,2,1-ij]quinoline derivatives, a 5-HT_{2C} receptor agonist with selectivity over the 5-HT_{2A} receptor: Potential therapeutic applications for epilepsy and obesity.* Bioorg Med Chem Lett 2000, 10(9): 919.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

291254

(+)-2,2-Dimethylpropionic acid 4-[2,5-dioxomorpholin-3(S)-ylmethyl]-2-hydroxyphenylester



C16 H19 N O6; Mol wt: 321.3271

ACTION – Levodopa prodrug with good lipophilicity (log P = 2.153), good aqueous solubility (50 µg/ml) and good chemical and enzymatic stability in aqueous buffer solution at pH 1.3 and 7.4; however, in 80% rat or human plasma, compound was rapidly converted to L-Dopa. Potentially useful for the treatment of Parkinson's disease.

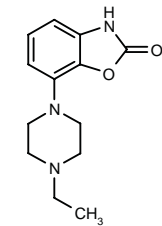
SOURCES – Università degli Studi di Camerino, Camerino (IT); Università degli Studi 'G. D'Annunzio', Chieti (IT).

REFERENCES

1. Gingolani, G.M. et al. *Synthesis of L-(+)-3-(3-hydroxy-4-pivaloyloxybenzyl)-2,5-diketomorpholine as potential prodrug of L-Dopa.* Bioorg Med Chem Lett 2000, 10(12): 1385.

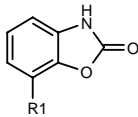
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Compound	R1	Formula
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SOURCE – Duphar.

REFERENCES

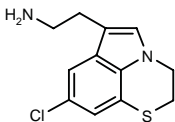
1. Toorop, G.P. et al. (Duphar International Research BV) *New piperazine and piperidine cpds.* WO 0029397.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

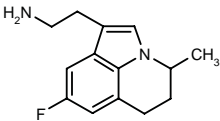
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290180: C14 H17 F N2

SOURCE – NPS Allelix.

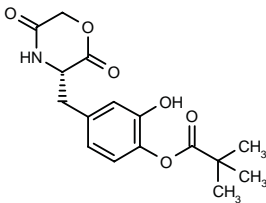
REFERENCES

1. Isaac, M. et al. *Pyrrolo[3,2,1-ij]quinoline derivatives, a 5-HT_{2C} receptor agonist with selectivity over the 5-HT_{2A} receptor: Potential therapeutic applications for epilepsy and obesity.* Bioorg Med Chem Lett 2000, 10(9): 919.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

291254

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SOURCES – Università degli Studi di Camerino, Camerino (IT); Università degli Studi 'G. D'Annunzio', Chieti (IT).

REFERENCES

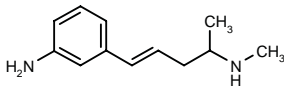
1. Gingolani, G.M. et al. *Synthesis of L-(+)-3-(3-hydroxy-4-pivaloyloxybenzyl)-2,5-diketomorpholine as potential prodrug of L-Dopa.* Bioorg Med Chem Lett 2000, 10(12): 1385.

COGNITION-ENHANCING DRUGS

289706

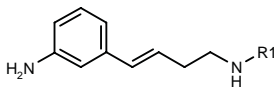
3-[4-Methylamino-1(*E*)-pentenyl]aniline

N-[4-(3-Aminophenyl)-1-methyl-3(*E*)-butenyl]-*N*-methylamine



C12 H18 N2; Mol wt: 190.2882

ACTION – Agent for the treatment of CNS disorders, particularly cognitive and neurodegenerative disorders, that acts as an agonist at certain nicotinic cholinergic receptor subtypes, exhibits good brain penetration and does not cause activation of receptors associated with undesirable side effects, particularly cardiovascular side effects. Compound gave a K_i value of 132 nM for neuronal nicotinic receptors and an EC_{50} value of 920 nM and an E_{max} value relative to (*S*)-(-)-nicotine of 78% for dopamine release, exhibiting high selectivity for neuronal receptors, as demonstrated by E_{max} values of 2 and 6%, respectively, at muscle-type and ganglionic-type receptors at a concentration of 100 μ M. Other specifically claimed compounds from this series of aryl substituted amine compounds are:



Compound	R1	Formula
289707	H	C ₁₀ H ₁₄ N ₂
289708	Me	C ₁₁ H ₁₆ N ₂

SOURCE – R.J. Reynolds Tobacco.

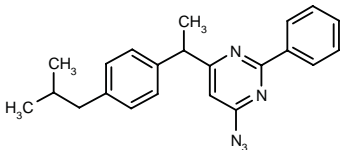
REFERENCES

1. Dull, G.M. et al. (R.J. Reynolds Tobacco Co.) *Pharmaceutical compsns. and methods for use*. WO 0023418.

290100

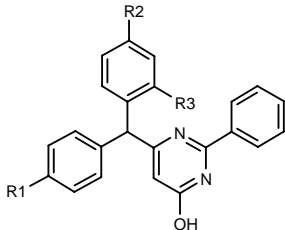
4-Azido-6-[1-(4-isobutylphenyl)ethyl]-2-phenylpyrimidine

6-[1-(4-Isobutylphenyl)ethyl]-2-phenyl-4-pyrimidinyl azide



C22 H23 N5; Mol wt: 357.4587

ACTION – An inhibitor of phospholipase A₂ (PLA₂), in particular cytosolic PLA₂ (cPLA₂), with potential in the treatment of cPLA₂-mediated conditions, particularly neurodegenerative diseases, cytokine-mediated diseases, conditions associated with arachidonic acid metabolites and dysfunctions of the inflammatory response. A representative compound from a series of substituted pyrimidine derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
290102	H	i-Bu	H	C ₂₇ H ₂₆ N ₂ O
290103	H	H	Et	C ₂₆ H ₂₂ N ₂ O
290105	H	Pr	H	C ₂₆ H ₂₄ N ₂ O
290106	i-Bu	H	Br	C ₂₇ H ₂₆ BrN ₂ O
290107	OEt	OEt	H	C ₂₇ H ₂₆ N ₂ O ₃

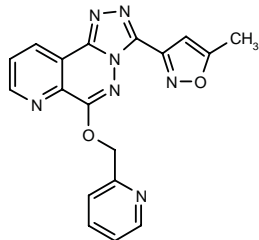
SOURCE – Elan.

REFERENCES

1. Varghese, J. et al. (Elan Pharmaceuticals) *Substd. pyrimidine compsns. and methods of use*. WO 0027824.

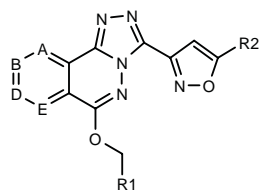
290369

3-(5-Methylisoxazol-3-yl)-6-(pyridin-2-ylmethoxy)pyrido-[3,2-*d*][1,2,4]triazolo[4,3-*b*]pyridazine



C18 H13 N7 O2; Mol wt: 359.3477

ACTION – Selective GABA_A receptor ligand that is reported to act as an inverse agonist at the $\alpha 5$ subtype (K_i = 100 nM or less), with potential in the treatment of cognitive disorders such as Alzheimer’s disease. Other exemplified compounds within this series of pentaaza-cyclopenta[*a*]naphthalene derivatives include the following:



Compound	R1	R2	A	B	D	E	Formula
290370	2-Pyr	Me	N	CH	CH	CH	C ₁₈ H ₁₃ N ₇ O ₂
290372	2-Pyr	Me	CH	CH	N	CH	C ₁₈ H ₁₃ N ₇ O ₂
290373	2-Pyr	Me	CH	N	CH	CH	C ₁₈ H ₁₃ N ₇ O ₂
290374	1-Me-1,2,4-triazol-5-yl	Me	CH	CH	CH	N	C ₁₈ H ₁₃ N ₉ O ₂
290375	1-Me-1,2,4-triazol-3-yl	OEt	CH	CH	CH	N	C ₁₇ H ₁₅ N ₉ O ₃
290377	1-Me-1,2,3-triazol-4-yl	Me	CH	CH	N	CH	C ₁₈ H ₁₃ N ₉ O ₂
290378	1-Me-1,2,4-triazol-3-yl	Me	CH	CH	N	CH	C ₁₈ H ₁₃ N ₉ O ₂
290380	3-CF3-2-Pyr	Me	CH	CH	N	CH	C ₁₉ H ₁₂ F ₃ N ₇ O ₂
290381	1-Me-1,2,3-triazol-4-yl	Me	CH	CH	-N(O)-	CH	C ₁₈ H ₁₃ N ₉ O ₃

SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Curtis, N.R. et al. (Merck Sharp & Dohme Ltd.) *Pentaaza-cyclopenta[a]naphthalene derivs. as ligands for GABA_A α₅ receptors*. WO 0029412.

508F(Fv)

290613

Mutant single-chain antibody constructed from variable regions of heavy and light chains of the anti-β-amyloid peptide IgM antibody 508, in which the cysteine residue in the complementarity-determining region CDR3 (residue 96) is replaced by phenylalanine

ACTION – Single-chain antibody directed against β-amyloid peptide (β-AP) with the ability to induce disaggregation of Alzheimer’s β-amyloid fibrils and prevent their toxic effects on cultured PC-12 cells. Potentially useful for the treatment of Alzheimer’s disease.

SOURCE – Tel Aviv University, Tel Aviv (IL).

REFERENCES

1. Frenkel, D. et al. *Modulation of Alzheimer’s β-amyloid neurotoxicity by site-directed single-chain antibody*. J Neuroimmunol 2000, 106(1-2): 23.

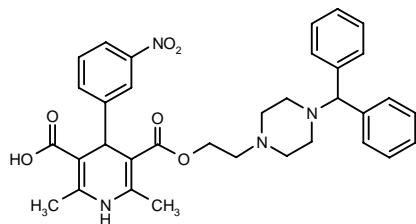
2. Frenkel, D. et al. *Modulation of Alzheimer’s β-amyloid neurotoxicity by site-directed single-chain antibody*. Neuroimmunomodulation 1999, 6(6): 444.

TREATMENT OF
CEREBROVASCULAR DISEASES

289549

5-[2-[4-(Diphenylmethyl)piperazin-1-yl]ethoxycarbonyl]-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid

2,6-Dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 2-[4-(diphenylmethyl)piperazin-1-yl]ethyl monoester



C34 H36 N4 O6; Mol wt: 596.6804

ACTION – A representative compound from a series dihydropyridines that antagonize N-type calcium channels and are thus useful for the treatment of encephalopathy due to acute ischemic states following brain infarction or brain hemorrhage and Alzheimer’s disease, among others.

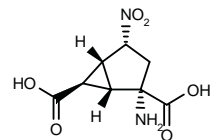
SOURCE – Ajinomoto.

REFERENCES

1. Niwa, S. et al. (Ajinomoto Co., Inc.) *Dihydropyridine derivs. and drug compsns. containing the same*. WO 0024716.

289838

(1S*,2S*,4R*,5R*,6S*)-2-Amino-4-nitrobicyclo[3.1.0]-hexane-2,6-dicarboxylic acid



C8 H10 N2 O6; Mol wt: 230.1750

ACTION – Metabotropic glutamate receptor modulator, a representative compound from a series of bicyclo[3.1.0]-hexane-2,6-dicarboxylic acid derivatives with potential for treating neurological disorders associated with glutamate dysfunction including cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord and head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, Alzheimer’s disease, Huntington’s chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage and retinopathy, cognitive disorders and idiopathic and drug-induced Parkinson’s disease.

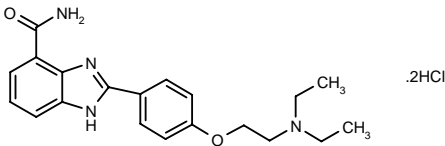
SOURCE – Lilly.

REFERENCES

1. Monn, J.A. and Valli, M.J. (Eli Lilly and Company) *Excitatory amino acid receptor modulators*. EP 1000927, WO 0029371.

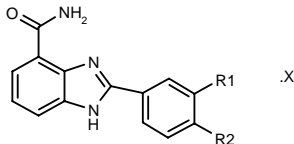
289858

2-[4-[2-(Diethylamino)ethoxy]phenyl]-1*H*-benzimidazole-4-carboxamide dihydrochloride



C20 H24 N4 O2 . 2HCl; Mol wt: 425.3574

ACTION – PARP (poly[ADP-ribose] polymerase, NAD⁺ ADP-ribosyltransferase) inhibitor with good aqueous solubility, potentially useful in the treatment of neurological and neurodegenerative disorders, renal and cardiovascular disorders, sepsis, cancer, immunological disorders and diabetes mellitus. Other exemplified compounds from this series of substituted 2-phenyl-benzimidazoles include the following:



Compound	R1	R2	R3	Formula
289859	t-BuOCONH(CH2)3O	H		C ₂₂ H ₂₆ N ₄ O ₄
289860	H	O(CH2)3N(Me)CH2Ph	2HCl	C ₂₅ H ₂₆ N ₄ O ₂ .2HCl
289861	3-(NH2CH2)-1-pyrrolyl	H		C ₁₉ H ₁₇ N ₅ O
289862	H	3-CHO-1-pyrrolyl		C ₁₉ H ₁₄ N ₄ O ₂
289863	H	4-[(Ph)2CH]-1-Piz		C ₃₁ H ₂₈ N ₅ O
289864	H	4-Et-perhydro-1,4-diazepin-1-yl		C ₂₁ H ₂₅ N ₅ O

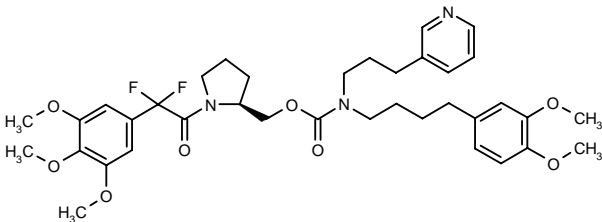
SOURCE – BASF.

REFERENCES

1. Lubisch, W. et al. (BASF AG) *Substd. 2-phenylbenzimidazoles, the production thereof and their use*. WO 0026192.

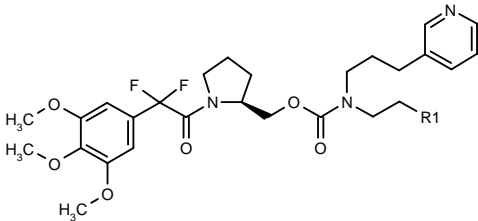
290085

N-[4-(3,4-Dimethoxyphenyl)butyl]-*N*-[3-(3-pyridyl)-propyl]carbamic acid 1-[2,2-difluoro-2-(3,4,5-trimethoxyphenyl)acetyl]pyrrolidin-2(*S*)-ylmethyl ester



C37 H47 F2 N3 O8; Mol wt: 699.7873

ACTION – Neurotrophic agent that binds to immunophilins such as the FK-506-binding protein FKBP12 and inhibits peptidylprolyl isomerase (PPIase or rotamase) activity, giving 98% inhibition at 1 μM. This nonimmunosuppressive compound is reported to stimulate neurite outgrowth in rat pheochromocytoma PC-12A cells, and may also be useful for reversing multidrug resistance (MDR) in cancer chemotherapy and in the treatment of HIV infection. Other exemplified compounds from this series of pyrrolidinemethyl diamide and carbamate derivatives include the following:



Compound	R1	Formula
290086	3-MeO-Ph	C ₃₄ H ₄₁ F ₂ N ₃ O ₇
290087	3,4-(MeO)2-Ph	C ₃₅ H ₄₃ F ₂ N ₃ O ₈
290088	3-CF3-Ph	C ₃₄ H ₃₈ F ₅ N ₃ O ₆
290089	4-CO2H-PhCH2	C ₃₅ H ₄₁ F ₂ N ₃ O ₈
290090	3-MeO-PhCH2	C ₃₅ H ₄₃ F ₂ N ₃ O ₇
290091	4-MeO-PhCH2	C ₃₅ H ₄₃ F ₂ N ₃ O ₇
290092	3,4,5-(MeO)3-PhCH2	C ₃₇ H ₄₇ F ₂ N ₃ O ₉

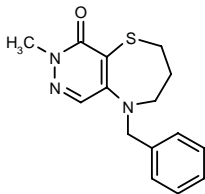
SOURCE – Bristol-Myers Squibb.

REFERENCES

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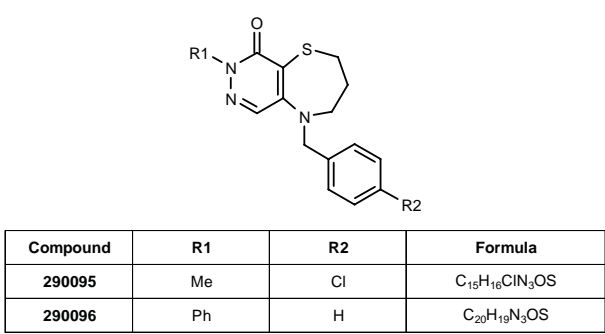
290094

5-Benzyl-8-methyl-2,3,4,5,8,9-hexahydropyridazino-[4,5-*b*][1,4]thiazepin-9-one



C15 H17 N3 O S; Mol wt: 287.3853

ACTION – Agent for the treatment of acute and chronic neurodegenerative diseases and for enhancing memory with NMDA-activating and AMPA-inhibiting activity. AMPA antagonism was demonstrated *in vitro* in a patch clamp test (64.46% inhibition of ion current at 100 μM in rat Purkinje cells) while NMDA-activating effects were shown in rat hippocampal cell cultures at 100 μM. *In vivo*, compound produced a 328% memory improvement compared to amnesic controls in the scopolamine-induced memory deficit passive avoidance test in rats at 50 mg/kg p.o. Other specifically claimed compounds from this series of condensed pyridazinone compounds are:



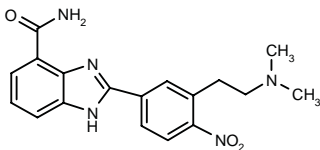
SOURCE – Gyogyszerkutato Intezet.

REFERENCES

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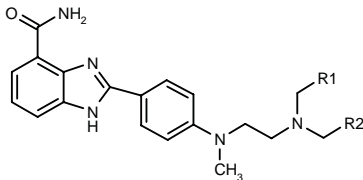
290280

2-[3-[2-(Dimethylamino)ethyl]-4-nitrophenyl]-1 H-benzimidazole-4-carboxamide



C18 H19 N5 O3; Mol wt: 353.3801

ACTION – An inhibitor of PARP (poly[ADP-ribose]-polymerase, NAD⁺ ADP-ribosyltransferase; K_i = 4 nM) with potential in the treatment of neurological and neurodegenerative disorders, renal and cardiovascular disorders, sepsis, cancer, immunological disorders and diabetes mellitus. Other specifically claimed compounds from this series of 2-phenylbenzimidazoles and 2-phenylindoles are:



Compound	R1	R2	Formula
290281	Me	Me	C ₂₁ H ₂₇ N ₅ O
290282	H	H	C ₁₉ H ₂₃ N ₅ O

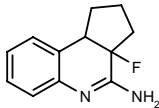
SOURCE – BASF.

REFERENCES

1. Lubisch, W. et al. (BASF AG) 2-Phenylbenzimidazoles and 2-phenylindoles, and production and use thereof. WO 0029384.

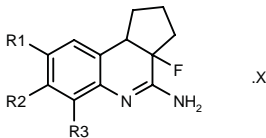
290305

3a-Fluoro-2,3,3a,9b-tetrahydro-1 H-cyclopenta[c]quinolin-4-amine



C12 H13 F N2; Mol wt: 204.2467

ACTION – Nitric oxide synthase (NOS) inhibitor with potential in the treatment of NO-mediated diseases such as neurodegenerative, inflammatory, autoimmune and cardiovascular disorders. Other specifically claimed compounds from this series of fluorinated 3,4-dihydroquinoline derivatives are:



Compound	R1	R2	R3	X	Formula
290309	H	H	F		C ₁₂ H ₁₂ F ₂ N ₂
290311	Br	H	H		C ₁₂ H ₁₂ BrFN ₂
290312	Cl	H	H		C ₁₂ H ₁₂ ClFN ₂
290314	H	CH ₂ NHMe	H	2HCl	C ₁₄ H ₁₈ FN ₃ ·2HCl
290315	H	CH ₂ CH ₂ NHMe	H	2HCl	C ₁₅ H ₂₀ FN ₃ ·2HCl
290317	H	3-Cl-PhCH ₂ NH(CH ₂) ₃	H	2HCl	C ₂₂ H ₂₅ ClFN ₃ ·2HCl

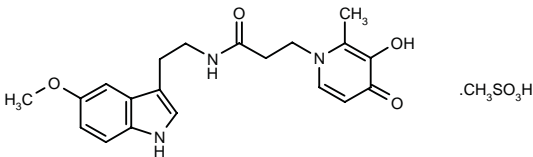
SOURCE – Schering AG.

REFERENCES

1. Jaro  ch, S. et al. (Schering AG) Fluorinated 3,4-dihydroquinoline derivs. used as NOS inhibitors. WO 0029381.

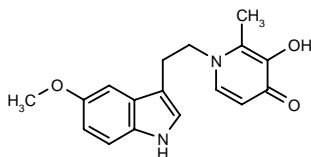
290318

3-(3-Hydroxy-2-methyl-4-oxo-1,4-hydropyridin-1-yl)-N-[2-(5-methoxy-1 H-indol-3-yl)ethyl]propionamide mesylate



C20 H23 N3 O4 . C H4 O3 S; Mol wt: 465.5243

ACTION – Antioxidant and reactive oxygen species (ROS) scavenger, a representative compound from a series of compounds combining in a single molecule a 3-hydroxy-2(1*H*)-pyridinone or a 3-hydroxy-4(1*H*)-pyridinone iron-chelating moiety and a phenolic antioxidant moiety; these compounds are reported to be more effective, especially at low concentrations *in vitro*, than the simultaneous use of an *ortho*-hydroxypyridone compound and a phenolic antioxidant. *In vitro*, compound inhibited lipid peroxidation in rat brain homogenates ($IC_{50} = 1.5 \mu M$) and protected cerebellar granule cells from iodoacetate-induced oxidative damage ($EC_{50} = 4.9 \mu M$). Potentially useful in the treatment of conditions associated with oxidative stress, particularly acute or chronic neurological disorders such as traumatic brain injury, spinal cord injury, cerebral tumor, subarachnoid hemorrhage, cerebral vasospasm, cerebral ischemia, stroke, Alzheimer's disease, Parkinson's disease, Friedrich's ataxia, motor neuron disease and multiple sclerosis. Another exemplified compound is:



290319: C17 H18 N2 O3

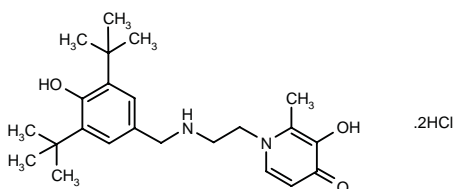
SOURCE – Vernalis Research.

REFERENCES

1. Bebbington, D. and Gaur, S. (Vernalis Research Ltd.) 3-Hydroxy-2(1*H*)-pyridinone or 3-hydroxy-4(1*H*)-pyridinone derivs. useful as reactive oxygen species (ROS) scavengers. EP 1006112.

290320

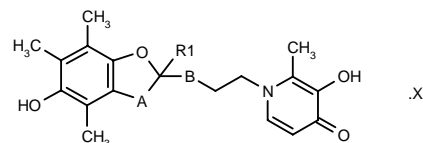
1-[2-(3,5-Di-*tert*-butyl-4-hydroxybenzylamino)ethyl]-3-hydroxy-2-methylpyridin-4(1*H*)-one dihydrochloride



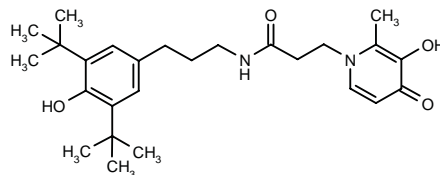
C23 H34 N2 O3 . 2HCl; Mol wt: 459.4544

ACTION – Antioxidant and reactive oxygen species (ROS) scavenger, a representative compound from a series of compounds combining in a single molecule a 3-hydroxy-2(1*H*)-pyridinone or a 3-hydroxy-4(1*H*)-pyridinone iron-chelating moiety and a phenolic antioxidant moiety; these compounds are reported to be more effective, especially at low concentrations *in vitro*, than the simultaneous use of an *ortho*-hydroxypyridone compound and a phenolic antioxidant. *In vitro*, compound inhibited lipid peroxidation in rat brain homogenates ($IC_{50} = 0.2 \mu M$) and protected cerebellar granule cells from iodoacetate-induced oxidative damage ($EC_{50} = 3.3 \mu M$). *In vivo*, it exhibited neuroprotective activity in a rat model of oxidative stress induced by malonic acid following intrastriatal injection. Potentially useful in the treatment of conditions associated with oxidative stress, particularly acute or chronic neurological disorders such as traumatic

brain injury, spinal cord injury, cerebral tumor, subarachnoid hemorrhage, cerebral vasospasm, cerebral ischemia, stroke, Alzheimer's disease, Parkinson's disease, Friedrich's ataxia, motor neuron disease and multiple sclerosis. Other exemplified compounds include the following:



Compound	R1	A	B	X	Formula
290324	Me	-(CH2)2-	-COO-		C ₂₂ H ₂₇ NO ₆
290325	Me	-(CH2)2-	-CONH-		C ₂₂ H ₂₈ N ₂ O ₅
290326	Me	-(CH2)2-	-CH2CONH-		C ₂₃ H ₃₀ N ₂ O ₅
290327	Me	-(CH2)2-	-CH2O-		C ₂₂ H ₂₉ NO ₅
290329	Me	-(CH2)2-	-CH2NHCH2CH2-	2HCl	C ₂₄ H ₃₄ N ₂ O ₄ .2HCl
290330	H	-CH2-	-CH2CONH-		C ₂₁ H ₂₆ N ₂ O ₅
290331	H	-CH2-	-CH2CO2-		C ₂₁ H ₂₅ NO ₆
290333	H	-CH2-	-CH2CH2OCO-		C ₂₂ H ₂₇ NO ₆



290322: C26 H38 N2 O4

SOURCE – Vernalis Research.

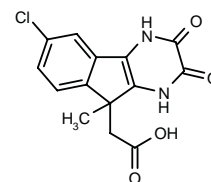
REFERENCES

1. Bebbington, D. et al. (Vernalis Research Ltd.) 3-Hydroxy-2(1*H*)-pyridinone or 3-hydroxy-4(1*H*)-pyridinone derivs. useful as reactive oxygen species (ROS) scavenger. EP 1006108.

RPR-118723*

278607

(-)-2-(6-Chloro-9-methyl-2,3-dioxo-2,3,4,9-tetrahydro-1*H*-indeno[1,2-*b*]pyrazin-9-yl)acetic acid



C14 H11 Cl N2 O4; Mol wt: 306.7039

ACTION – Optically active, water-soluble glycine/NMDA receptor antagonist with nanomolar affinity for this receptor site ($IC_{50} = 5$ nM against [3H]-DCKA binding in rat cortical membranes) and very weak affinity for AMPA receptors ($IC_{50} = 10$ μ M) and glutamate and TCP binding sites on the NMDA receptor ($IC_{50} = 5.2$ and 25 μ M, respectively). In addition, compound strongly inhibited ($IC_{50} = 3.5$ nM) the increase in [3H]-TCP binding in the presence of NMDA and concentration-dependently antagonized the NMDA-induced increase in [3H]-dopamine release from mouse striatal slices ($IC_{50} = 8$ nM); both these effects are reversed by an excess of glycine. NMDA-activated currents were concentration-dependently antagonized in rat cerebral neurons with an IC_{50} of 1.9 nM and it provided dose-dependent block of long-term potentiation (LTP) in rat brain at doses of 0.3 - 30 mg/kg i.v. The compound displayed anticonvulsant activity in the maximal electro-shock seizure assay in mice ($ED_{50} = 4.5$ mg/kg i.p., 2.0 mg/kg i.v.). Potentially useful for the treatment of cerebral ischemia and neurotrauma.

SOURCE – Aventis Pharma.

REFERENCES

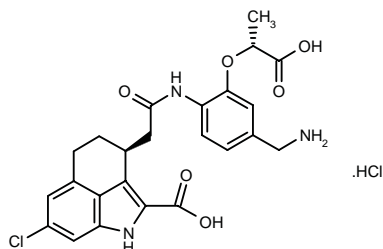
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- Boireau, A. et al. *Effects of RPR 118723, a novel antagonist at the glycine site of the NMDA receptor, in vitro*. Eur J Pharmacol 2000, 401(2): 131.
- Jimonet, P. et al. *Indeno[1,2-b]pyrazin-2,3-diones: A new class of antagonists at the glycine site of the NMDA receptor with potent in vivo activity*. J Med Chem 2000, 43(12): 2371.
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- Jimonet, P. et al. *RPR 118723: A new antagonist at the glycine site of the NMDA receptor-channel complex with potent central activity*. 26th Natl Med Chem Symp (June 14-18, Richmond) 1998, Abst D-23.

*Identified compound **278607** (see **278601**) Drug Data Rep 1999, 021(09): 0776.

SM-31900

287183

3(*S*)-[2-[4-(Aminomethyl)-2-[1(*R*)-carboxyethoxy]phenyl-amino]-2-oxoethyl]-7-chloro-1,3,4,5-tetrahydrobenzo[*c,d*]-indole-2-carboxylic acid hydrochloride



C24 H24 Cl N3 O6 . HCl; Mol wt: 522.3825

ACTION – Glycine-site NMDA receptor antagonist with high affinity for this site ($K_i = 1$ and 10 nM for displacement of [3H]-DCKA and [3H]-glycine binding, respectively, in rat brain membranes), proven to completely prevent [3H]-MK-801 binding in rat brain membranes. In primary cultures of rat cortical neurons, compound prevented glutamate-induced neurotoxicity with a potency about 240-fold higher than that of DCKA. Moreover, it was able to protect against NMDA-induced seizures in mice ($ED_{50} = 2.3$ mg/kg i.v.). Potentially useful for the treatment of cerebral ischemia (stroke) and epilepsy.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

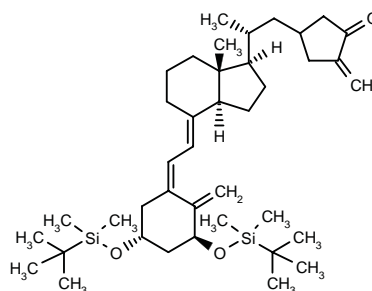
- Ae, N. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Tricyclic indole-2-carboxylic acid cpd. used as NMDA receptor antagonist*. WO 0056711.
- Katayama, S. et al. *Tricyclic indole-2-carboxylic acids, highly in vivo active antagonists for the glycine binding site of the NMDA receptor*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 215.
- Ohtani, K. et al. *Pharmacological properties of SM-31900, a novel NMDA receptor glycine-binding site antagonist*. Jpn J Pharmacol 2000, 82(Suppl. 1): Abst O-271.
- SM-31900 emerges as a promising therapeutic for stroke*. DailyDrugNews.com (Daily Essentials) 2000, June 28.

RESPIRATORY DRUGS

ASTHMA THERAPY

289538

3-*O*-(*tert*-Butyldimethylsilyl)-1 α -(*tert*-butyldimethylsilyloxy)-22-(4-methylene-3-oxocyclopentyl)-23,24,25,26,27-pentanorvitamin D₃ isomer B



C40 H68 O3 Si2; Mol wt: 653.1462

ACTION – Vitamin D₃ derivative useful for the treatment of inflammatory respiratory diseases, cancer, rheumatism, osteoporosis, diabetes, hypertension, alopecia, acne, psoriasis, dermatitis, hypercalcemia and cartilage metabolic disorders. Compound was found to potently antagonize the ability of $1\alpha,25$ -hydroxyvitamin D₃ to induce differentiation of HL-60 cells in the nitroblue tetrazolium (NBT) reduction assay at a concentration of 0.1 μ M and it produced 20-40% inhibition of neutrophil infiltration in a hamster model of lipopolysaccharide-induced pneumonia at 1 μ g/kg intratracheally. Other exemplified compounds include the following:

ACTION – Optically active, water-soluble glycine/NMDA receptor antagonist with nanomolar affinity for this receptor site ($IC_{50} = 5$ nM against [3H]-DCKA binding in rat cortical membranes) and very weak affinity for AMPA receptors ($IC_{50} = 10$ μ M) and glutamate and TCP binding sites on the NMDA receptor ($IC_{50} = 5.2$ and 25 μ M, respectively). In addition, compound strongly inhibited ($IC_{50} = 3.5$ nM) the increase in [3H]-TCP binding in the presence of NMDA and concentration-dependently antagonized the NMDA-induced increase in [3H]-dopamine release from mouse striatal slices ($IC_{50} = 8$ nM); both these effects are reversed by an excess of glycine. NMDA-activated currents were concentration-dependently antagonized in rat cerebral neurons with an IC_{50} of 1.9 nM and it provided dose-dependent block of long-term potentiation (LTP) in rat brain at doses of 0.3 - 30 mg/kg i.v. The compound displayed anticonvulsant activity in the maximal electro-shock seizure assay in mice ($ED_{50} = 4.5$ mg/kg i.p., 2.0 mg/kg i.v.). Potentially useful for the treatment of cerebral ischemia and neurotrauma.

SOURCE – Aventis Pharma.

REFERENCES

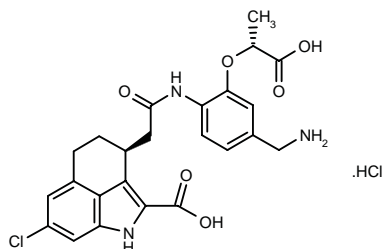
- Aloup, J.-C. et al. (Aventis Pharma SA) *5H-Indeno[1,2-b]pyrazine-2,3-dione derivs., their preparation and medicinal products containing them*. US 5922716, WO 9526342.
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*Identified compound **278607** (see **278601**) Drug Data Rep 1999, 021(09): 0776.

SM-31900

287183

3(*S*)-[2-[4-(Aminomethyl)-2-[1(*R*)-carboxyethoxy]phenyl-amino]-2-oxoethyl]-7-chloro-1,3,4,5-tetrahydrobenzo[*c,d*]-indole-2-carboxylic acid hydrochloride



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SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

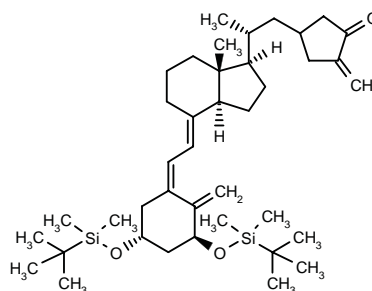
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- SM-31900 emerges as a promising therapeutic for stroke*. DailyDrugNews.com (Daily Essentials) 2000, June 28.

RESPIRATORY DRUGS

ASTHMA THERAPY

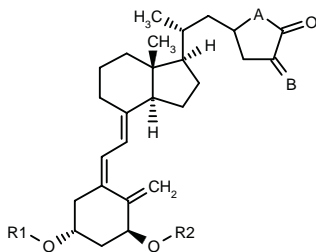
289538

3-*O*-(*tert*-Butyldimethylsilyl)-1 α -(*tert*-butyldimethylsilyloxy)-22-(4-methylene-3-oxocyclopentyl)-23,24,25,26,27-pentanorvitamin D₃ isomer B



C40 H68 O3 Si2; Mol wt: 653.1462

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Compound	R1=R2	A	B	Isomer	Formula
289540	t-BuSi(Me)2	CH2	CH2	A	C ₄₀ H ₆₈ O ₃ Si ₂
289541	t-BuSi(Me)2	C(=CH2)	H2	A	C ₄₀ H ₆₈ O ₃ Si ₂
289542	H	NH	CH2	B	C ₂₇ H ₃₉ NO ₃

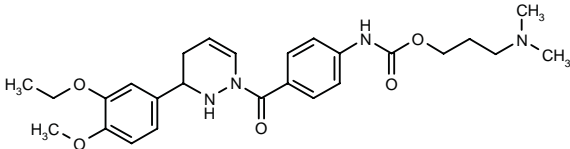
SOURCE – Teijin.

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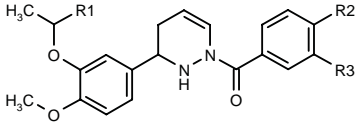
289718

N-[4-[3-(3-Ethoxy-4-methoxyphenyl)-1,2,3,4-tetrahydropyridazin-1-ylcarbonyl]phenyl]carbamic acid 3-(dimethyl-amino)propyl ester



C26 H34 N4 O5; Mol wt: 482.5776

ACTION – An inhibitor of phosphodiesterase type 4 (PDE4) and of the production of TNF, with potential in the treatment of osteoporosis, tumors, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, ulcerative colitis, inflammatory processes, allergies, asthma, autoimmune diseases, AIDS and transplant rejection. Other specifically claimed compounds from this series of benzoylpyridazines are:



Compound	R1	R2	R3	Formula
289719	H	1-Me-4-Pip-OC(=O)NH	H	C ₂₇ H ₃₄ N ₄ O ₅
289720	Me	NHCO2(CH2)3N(Me)2	H	C ₂₇ H ₃₆ N ₄ O ₅
289721	H	H	NHCO2(CH2)3N(Me)2	C ₂₆ H ₃₄ N ₄ O ₅

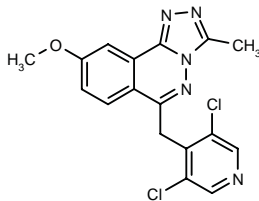
SOURCE – Merck KGaA.

REFERENCES

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289731

6-(3,5-Dichloropyridin-4-ylmethyl)-9-methoxy-3-methyl-[1,2,4]triazolo[3,4-a]phthalazine



C17 H13 Cl2 N5 O; Mol wt: 374.2297

ACTION – A representative compound from a series of tricyclic phthalazine derivatives that inhibits phosphodiesterase type 4 (PDE4) activity and TNF-α release (IC₅₀ = 207 nM against PDE4 from human polymorphonuclear leukocytes). Particularly useful for the treatment of allergic and inflammatory respiratory diseases.

SOURCE – Zambon.

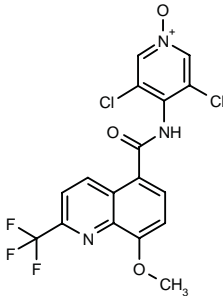
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289736

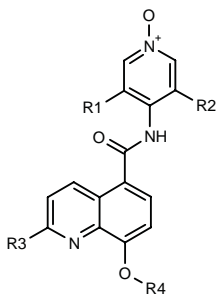
3,5-Dichloro-4-[8-methoxy-2-(trifluoromethyl)quinolin-5-ylcarboxamido]pyridine-1-oxide

N-(3,5-Dichloro-1-oxidopyridin-4-yl)-8-methoxy-2-(trifluoromethyl)quinoline-5-carboxamide



C17 H10 Cl2 F3 N3 O3; Mol wt: 432.1840

ACTION – A representative compound from a series of N-oxide derivatives of previously reported phosphodiesterase type 4 (PDE 4) and TNF production inhibitors that exhibit superior solubility and metabolic stability and an improved pharmacokinetic profiles. Compound displayed significantly increased C_{max} and AUC values and a longer half-life (t_{1/2} = 20 h vs. 4.5 h) as compared to the corresponding free base following administration of 3 mg/kg p.o. to rats. In addition, its solubility in water was about 100-fold higher than that of the parent compound. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	Formula
289737	H	Cl	Me	CHF2	C ₁₇ H ₁₂ ClF ₂ N ₃ O ₃
289738	H	Cl	CF3	CHF2	C ₁₇ H ₉ ClF ₅ N ₃ O ₃
289739	H	Cl	CF3	Me	C ₁₇ H ₁₁ ClF ₃ N ₃ O ₃
289741	F	F	CF3	Me	C ₁₇ H ₁₀ F ₅ N ₃ O ₃
289742	F	F	CF3	CHF2	C ₁₇ H ₈ F ₇ N ₃ O ₃
289743	H	Me	CF3	CHF2	C ₁₈ H ₁₂ F ₃ N ₃ O ₃
289744	Me	Me	CF3	Me	C ₁₉ H ₁₆ F ₃ N ₃ O ₃
289747	Cl	Cl	CF3	CHF2	C ₁₇ H ₈ Cl ₂ F ₃ N ₃ O ₃
289748	H	Me	Me	CHF2	C ₁₈ H ₁₅ F ₂ N ₃ O ₃
289749	H	Me	CF3	Me	C ₁₈ H ₁₄ F ₃ N ₃ O ₃

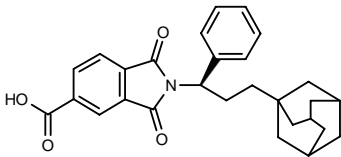
SOURCE – Darwin Discovery.

REFERENCES

1. Dyke, H.J. and Montana, J.G. (Darwin Discovery Ltd.) *N*-Oxides of heterocyclic cpds. with TNF and PDE-IV inhibiting activity. WO 0026208.

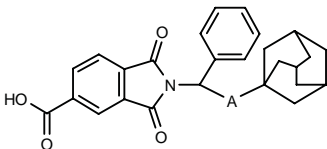
289912

2-[3-(1-Adamantyl)-1(*R*)-phenylpropyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid



C28 H29 N O4; Mol wt: 443.5401

ACTION – Antiallergic agent that acts by inhibiting the production of IgE (IC₅₀ = 0.60 μM in lipopolysaccharide-stimulated murine spleen mononuclear cells) and IL-5 (IC₅₀ = 0.90 μM in anti-CD3 antibody-stimulated human peripheral blood mononuclear cells). Other compounds from this series of phthalimide derivatives include the following:



Compound	A	Isomer	Formula
289913	-CH2OCH2-	S	C ₂₈ H ₂₉ NO ₅
289914	-CH2-		C ₂₇ H ₂₇ NO ₄

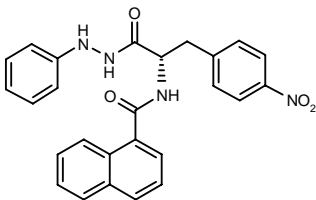
SOURCE – Japan Tobacco.

REFERENCES

1. Kawasaki, H. et al. (Japan Tobacco Inc.) *Phthalimide cpds., and medicines containing the same.* JP 2000128862.

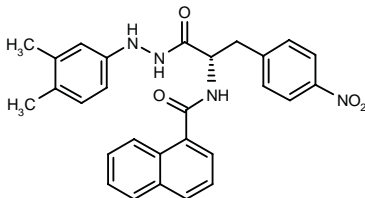
289999

N-[1(*S*)-(4-Nitrobenzyl)-2-oxo-2-(2-phenylhydrazino)-ethyl]naphthalene-1-carboxamide



C26 H22 N4 O4; Mol wt: 454.4838

ACTION – Chemokine CCR3 receptor antagonist, potentially useful in the treatment of asthma, eczema, allergic rhinitis, conjunctivitis, nasal polyposis, atopic dermatitis, pruritus and inflammatory bowel disease. Another specifically claimed acyl hydrazine derivative is



290000: C28 H26 N4 O4

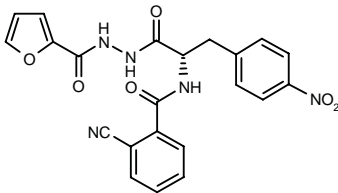
SOURCE – SmithKline Beecham.

REFERENCES

1. Dhanak, D. and Darcy, M.G. (SmithKline Beecham Corp.) *CCR-3 receptor antagonists.* WO 0027843.

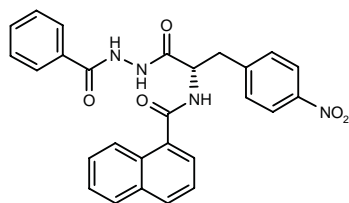
290001

2-Cyano-*N*-[2-[2-(2-furylcarbonyl)hydrazino]-1(*S*)-(4-nitrobenzyl)-2-oxoethyl]benzamide



C22 H17 N5 O6; Mol wt: 447.4053

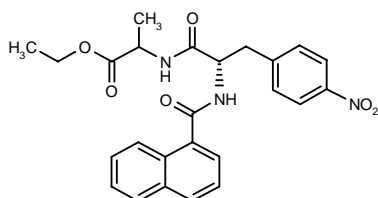
ACTION – Chemokine CCR3 receptor antagonist, potentially useful in the treatment of asthma, eczema, allergic rhinitis, conjunctivitis, nasal polyposis, atopic dermatitis, pruritus and inflammatory bowel disease. Another specifically claimed diacyl hydrazine derivative is:

**290002:** C27 H22 N4 O5**SOURCE** – SmithKline Beecham.**REFERENCES**

1. Dhanak, D. and Darcy, M.G. (SmithKline Beecham Corp.) *CCR-3 receptor antagonists*. WO 0027835.

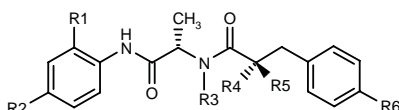
290003

2-[2(S)-(1-Naphthylcarboxamido)-3-(4-nitrophenyl)-propionamido]propionic acid ethyl ester



C25 H25 N3 O6; Mol wt: 463.4875

ACTION – Chemokine CCR3 receptor antagonist, potentially useful in the treatment of asthma, eczema, allergic rhinitis, conjunctivitis, nasal polyposis, atopic dermatitis, pruritus and inflammatory bowel disease. Other specifically claimed phenylalanine amide derivatives include the following:



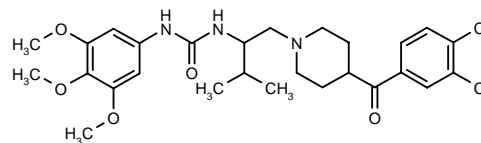
Compound	R1	R2	R3	R4	R5	R6	Formula
290005	H	H	H	1-Naph-CONH	H	Cl	C ₂₉ H ₂₆ ClN ₃ O ₃
290006	H	H	Me	1-Naph-CONH	H	NO ₂	C ₃₀ H ₂₈ N ₄ O ₅
290007	H	Ac	H	1-Naph-CONH	H	Cl	C ₃₁ H ₂₈ ClN ₃ O ₄
290008	H	Cl	H	H	2,4-(Me)2-Ph	Cl	C ₂₈ H ₂₆ Cl ₂ N ₂ O ₂
290009	OMe	H	H	1-Naph-CONH	H	OMe	C ₃₁ H ₃₁ N ₃ O ₅

SOURCE – SmithKline Beecham.**REFERENCES**

1. Dhanak, D. (SmithKline Beecham Corp.) *CCR-3 receptor antagonists*. WO 0027800.

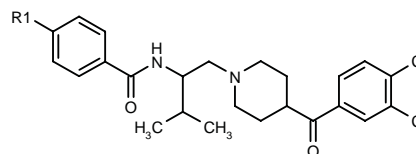
290277

N-[1-[4-(3,4-Dichlorobenzoyl)piperidin-1-ylmethyl]-2-methylpropyl]-N'-(3,4,5-trimethoxyphenyl)urea



C27 H35 Cl2 N3 O5; Mol wt: 552.4955

ACTION – Chemokine CCR3 receptor antagonist that is capable of inhibiting the binding of eotaxin to the CCR3 receptor and is thus expected to be useful in the treatment of eosinophil-mediated inflammatory disorders, particularly asthma. Other exemplified compounds from this series of 4-arylpiperidine derivatives are:



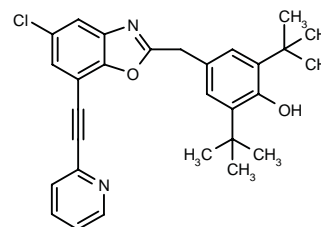
Compound	R1	Formula
290278	OMe	C ₂₅ H ₃₀ Cl ₂ N ₂ O ₃
290279	Me	C ₂₅ H ₃₀ Cl ₂ N ₂ O ₂

SOURCE – Roche.**REFERENCES**

1. Gong, L. et al. (F. Hoffmann-La Roche AG) *4-Aroyl-piperidin-CCR-3 receptor antagonists III*. WO 0029377.

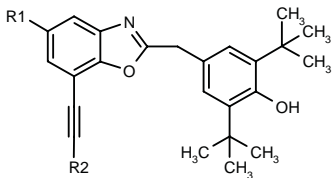
290308

4-[5-Chloro-7-[2-(2-pyridinyl)ethynyl]benzoxazol-2-ylmethyl]-2,6-di-*tert*-butylphenol



C29 H29 Cl N2 O2; Mol wt: 473.0131

ACTION – Selective phosphodiesterase type 4 (PDE4) inhibitor with bronchodilating and antiinflammatory properties, being more active than rolipram and theophylline and exhibiting higher selectivity. *In vitro*, it gave IC₅₀ values of 0.013 μ M against PDE4 and > 300 μ M against PDE3 and PDE5. Other exemplified compounds with 6,5-fused aromatic ring systems are:



Compound	R1	R2	Formula
290310	H	2-Pyr	C ₂₉ H ₃₀ N ₂ O ₂
290313	Cl	2-thiazolyl	C ₂₇ H ₂₇ ClN ₂ O ₂ S
290316	Cl	CH ₂ OH	C ₂₅ H ₂₆ ClNO ₃

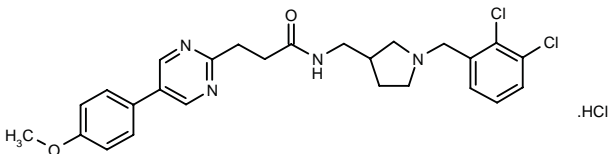
SOURCE – Euroceltique.

REFERENCES

1. Chasin, M. et al. (Euroceltique SA) *6,5-Fused aromatic ring systems having enhanced phosphodiesterase IV inhibitory activity*. US 6075016.

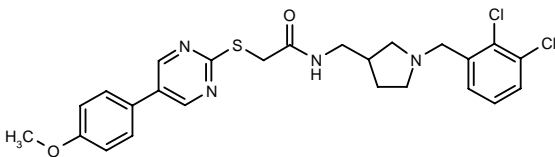
290481

N-[1-(2,3-Dichlorobenzyl)pyrrolidin-3-ylmethyl]-3-[5-(4-methoxyphenyl)pyrimidin-2-yl]propionamide hydrochloride



C26 H28 Cl2 N4 O2 . HCl; Mol wt: 535.9001

ACTION – Chemokine CCR3 receptor antagonist that is capable of inhibiting the binding of eotaxin to the CCR3 receptor and is thus expected to be useful in the treatment of eosinophil-mediated inflammatory disorders, particularly asthma. Another exemplified compound from this series of pyrrolidine derivatives is:



290482: C25 H26 Cl2 N4 O2 S

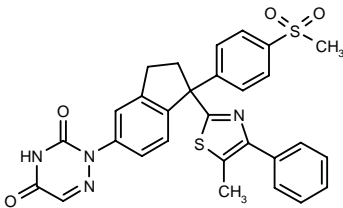
SOURCE – Roche.

REFERENCES

1. Rogers, D.H. et al. (F. Hoffmann-La Roche AG) *Pyrrolidine derivs.-CCR-3 receptor antagonists*. WO 0031032.

290498

2-[1-(5-Methyl-4-phenylthiazol-2-yl)-1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1 H-inden-5-yl]-1,2,4-triazine-3,5(2H,4H)-dione



C29 H24 N4 O4 S2; Mol wt: 556.6646

ACTION – An inhibitor of the production of IL-5 (39% inhibition at 1 µM in human peripheral blood) also reported to inhibit the production of other chemokines such as MCP-1 and MCP-3, while having little or no effect on the production of IL-1, IL-2, IL-3, IL-4, IL-6, IL-10, interferon gamma and GM-CSF. Potentially useful for the treatment of eosinophil-dependent inflammatory diseases, particularly bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis. A representative compound from a series of 6-azauracil derivatives.

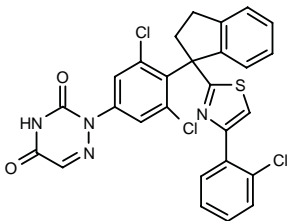
SOURCE – Janssen.

REFERENCES

1. Freyne, E.J.E. et al. (Janssen Pharmaceutica NV) *IL-5 inhibiting 6-azauracil derivs*. WO 0031054.

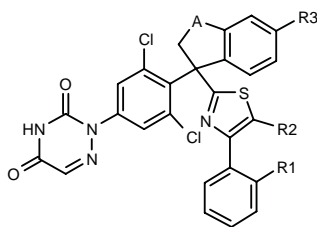
290499

2-[3,5-Dichloro-4-[1-[4-(2-chlorophenyl)thiazol-2-yl]-2,3-dihydro-1 H-inden-1-yl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione



C27 H17 Cl3 N4 O2 S; Mol wt: 567.8823

ACTION – An inhibitor of the production of IL-5 (94% inhibition at 1 µM in human peripheral blood) also reported to inhibit the production of other chemokines such as MCP-1 and MCP-3, while having little or no effect on the production of IL-1, IL-2, IL-3, IL-4, IL-6, IL-10, interferon gamma and GM-CSF. Potentially useful for the treatment of eosinophil-dependent inflammatory diseases, particularly bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis. Other compounds from this series of 6-azauracil derivatives include the following:



Compound	R1	R2	R3	A	Formula
290501	H	Me	H	-CH2-	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₂ S
290504	H	Ph	H	-CH2-	C ₃₃ H ₂₂ Cl ₂ N ₄ O ₂ S
290505	H	H	H	-CH2-	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂ S
290506	H	CO ₂ Et	H	-CH2-	C ₃₀ H ₂₂ Cl ₂ N ₄ O ₄ S
290507	H	Me	H	-CH ₂ O-	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃ S
290508	Cl	H	Cl	-CH2-	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂ S

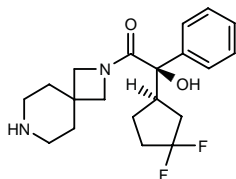
SOURCE – Janssen.

REFERENCES

1. Lacrampe, J.F.A. et al. (Janssen Pharmaceutica NV) *IL-5 inhibiting 6-azauracil derivs.* WO 0031053.

290560

1-(2,7-Diazaspiro[3.5]non-2-yl)-2(*R*)-[3,3-difluoro-1(*R*)-cyclopentyl]-2-hydroxy-2-phenyl-1-ethanone



C₂₀ H₂₆ F₂ N₂ O₂; Mol wt: 364.4334

ACTION – Agent for the treatment of respiratory, urological and digestive disorders, a potent and selective muscarinic M₃ receptor antagonist, as demonstrated in binding studies (K_i = 1.9 nM vs. 180 nM for M₂ receptors; ratio M₂/M₃ = 93) and in functional assays measuring the inhibition of carbachol-induced contractions (K_B = 0.98 nM in rat trachea [M₃] vs. 83 nM in rat right atrium [M₂]; ratio M₂/M₃ = 85). *In vivo*, compound exhibited good bronchodilating activity in the methacholine inhalation test in dogs at 0.1 mg/kg p.o. A representative compound from a series of 1-acylazetidione derivatives.

SOURCE – Banyu.

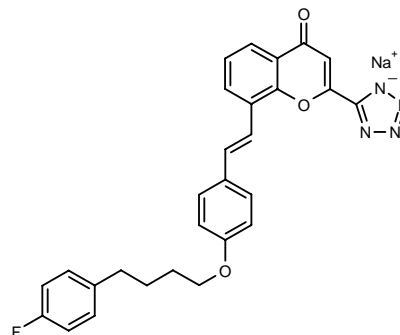
REFERENCES

1. Tsuchiya, Y. et al. (Banyu Pharmaceutical Co., Ltd.) *1-Acy lazetidione derivs.* WO 0031078.

LM-1507.Na

290497

(*E*)-8-[2-[4-[4-(4-Fluorophenyl)butoxy]phenyl]vinyl]-2-(1*H*-tetrazol-5-yl)-4*H*-benzopyran- 4-one sodium salt



C₂₈ H₂₂ F N₄ Na O₃; Mol wt: 504.4948

ACTION – Potent and selective CysLT₁ receptor antagonist with potent activity against specific [³H]-LTD₄ binding, as demonstrated by K_i values of 0.65, 0.50 and 31 nM, respectively, in differentiated U937 cells (montelukast = 0.6 nM), guinea pig lung membranes and human lung membranes; it also exhibited potent activity against [³H]-LTE₄ binding (K_i = 0.1 nM in guinea pig lung membranes) but was inactive against [³H]-LTC₄ binding (K_i > 1000 nM) and 30 different receptor subtypes including adenosine, histamine, PAF, PGI₂, TxA₂, NK₁ and NK₂ receptors. In a functional assay in U937 cells, compound and montelukast uncompetitively antagonized calcium mobilization induced by LTD₄ (pK_b = 10.2 vs. 9.42). Compound furthermore inhibited LTD₄-induced contractions of isolated human bronchi (pA₂ = 8.13) and was effective against LTD₄-induced bronchoconstriction in anesthetized guinea pigs following both i.v. (ED₅₀ = 3.0 nmol/kg) and oral (ED₅₀ = 0.14 μmol/kg) doses. It completely inhibited LTD₄-induced microvascular leakage in guinea pig trachea for up to 8 h when given as 1-h pretreatment at a dose of 48 μmol/kg p.o. Pharmacokinetic and distribution studies in rats showed linear pharmacokinetics upon single oral doses in the range 50-1000 mg/kg. Although AUC values after oral doses were similar to those with montelukast, the AUC after i.v. administration was 10 times higher than for montelukast at the same dose. Potentially useful for the treatment of asthma.

SOURCE – Menarini.

REFERENCES

1. Carganico, G. et al. (Laboratorios Menarini SA) *Benzopyran derivs. having leukotriene-antagonistic action.* EP 0888327, ES 2127106, JP 2000506878, US 5990142, WO 9734885.

2. Cabré, F. et al. *Pharmacological profile of the new orally active and selective Cys-LT₁ receptor antagonist LM-1507.Na.* 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 82.

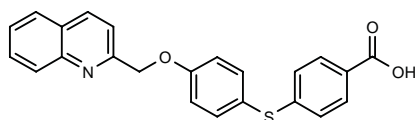
3. Cucchi, P. et al. *Pharmacological effects of LM-1507.Na, a new potent Cys-LT₁ receptor antagonist, in DMSO-differentiated U937 cells.* 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 82.

4. Tost, D. et al. *Preliminary pharmacokinetic and distribution studies of the new Cys-LT₁ antagonist LM-1507.Na, after a single administration to rats.* 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 82.

VUFB-19363

290488

4-[4-(2-Quinolinylmethoxy)phenylsulfanyl]benzoic acid



C23 H17 N O3 S; Mol wt: 387.4573

ACTION – Antiinflammatory and antiasthmatic agent able to inhibit the production of LTB_4 in rat polymorphonuclear cells ($\text{IC}_{50} = 4 \text{ nM}$). Compound exhibited nanomolar affinity for the LTD_4 receptor ($\text{IC}_{50} = 24 \text{ nM}$) and lower affinity for the LTB_4 (BLT) receptor ($\text{IC}_{50} = 91.6 \text{ }\mu\text{M}$). Significant antiinflammatory and antiasthmatic activity was seen *in vivo*, superior to that of the leukotriene synthesis inhibitor zileuton.

SOURCE – Research Institute of Pharmacy and Biochemistry (VUFB), Prague (CZ).

REFERENCES

1. Kuchar, M. et al. (Research Institute of Pharmacy and Biochemistry [VUFB]) *Derivs. of hydroxyphenylsulfanylbenzoic and hydroxyphenylsulfanyllarylacetic acids*. WO 9967208.

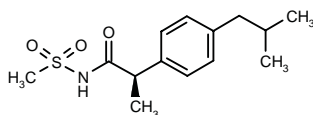
2. Kuchar, M. et al. *The derivatives of arylsulfanyl benzoic acids with multiple antileukotrienic activities*. 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 82.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

DF-1681

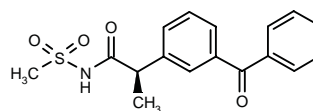
289580

2(R)-(4-Isobutylphenyl)-N-(methylsulfonyl)propionamide



C14 H21 N O3 S; Mol wt: 283.3899

ACTION – An inhibitor of neutrophil chemotaxis and degranulation induced by IL-8, as demonstrated *in vitro* by concentration-dependent inhibition of IL-8-induced chemotaxis of human polymorphonuclear (PMN) leukocytes in the concentration range from 0.01 nM to 1 μM , with potential in the treatment of neutrophil-dependent pathologies such as acute respiratory distress syndrome (ARDS), idiopathic fibrosis, ischemia and reperfusion damage, psoriasis, rheumatoid arthritis, ulcerative colitis and glomerulonephritis. Another compound from this series of *N*-(2-arylpropionyl)-sulfonamides is:



DF-1661 [289581]: C17 H17 N O4 S

SOURCE – Dompé.

REFERENCES

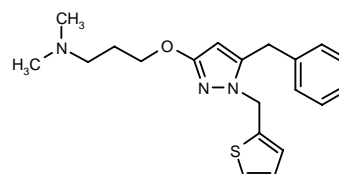
1. Bertini, R. et al. (Dompé Farmaceutici SpA) *N*-(2-Aryl-propionyl)-sulfonamides and pharmaceutical preparations containing them. WO 0024710.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

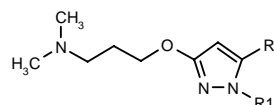
290191

N-[3-[5-Benzyl-1-(2-thienylmethyl)-1*H*-pyrazol-3-yloxy]-propyl]-*N,N*-dimethylamine



C20 H25 N3 O S; Mol wt: 355.5035

ACTION – Soluble guanylate cyclase (sGC) activator with vasodilating and platelet aggregation-inhibitory activity, potentially useful for the treatment or prevention of peripheral vascular diseases such as hypertension, angina pectoris and arteriosclerosis, as well as for the treatment or prevention of glaucoma, preeclampsia, Raynaud's syndrome, stroke and erectile dysfunction. *In vitro*, compound produced potent stimulation of recombinant sGC at a concentration of 1 μM and inhibited collagen-induced aggregation of human platelet-rich plasma with an IC_{50} value of 0.5 μM . Other exemplified compounds from this series of pyrazole and indazole derivatives include the following:

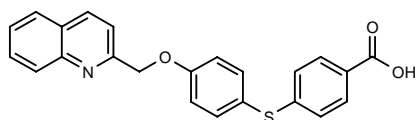


Compound	R1	R2	Formula
290193	Ph	Ph	C ₂₀ H ₂₃ N ₃ O
290194	3,4-(Cl)2-PhCH ₂	CH ₂ Ph	C ₂₂ H ₂₅ Cl ₂ N ₃ O
290195	3-Br-PhCH ₂	CH ₂ Ph	C ₂₂ H ₂₆ BrN ₃ O
290196	2-Cl-PhCH ₂	CH ₂ Ph	C ₂₂ H ₂₆ ClN ₃ O

VUFB-19363

290488

4-[4-(2-Quinolinylmethoxy)phenylsulfanyl]benzoic acid



C23 H17 N O3 S; Mol wt: 387.4573

ACTION – Antiinflammatory and antiasthmatic agent able to inhibit the production of LTB₄ in rat polymorphonuclear cells (IC₅₀ = 4 nM). Compound exhibited nanomolar affinity for the LTD₄ receptor (IC₅₀ = 24 nM) and lower affinity for the LTB₄ (BLT) receptor (IC₅₀ = 91.6 μM). Significant antiinflammatory and antiasthmatic activity was seen *in vivo*, superior to that of the leukotriene synthesis inhibitor zileuton.

SOURCE – Research Institute of Pharmacy and Biochemistry (VUFB), Prague (CZ).

REFERENCES

1. Kuchar, M. et al. (Research Institute of Pharmacy and Biochemistry [VUFB]) *Derivs. of hydroxyphenylsulfanylbenzoic and hydroxyphenylsulfanylarylacetic acids*. WO 9967208.

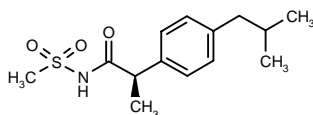
2. Kuchar, M. et al. *The derivatives of arylsulfanyl benzoic acids with multiple antileukotrienic activities*. 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 82.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

DF-1681

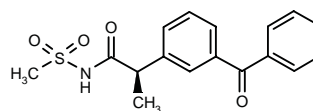
289580

2(R)-(4-Isobutylphenyl)-N-(methylsulfonyl)propionamide



C14 H21 N O3 S; Mol wt: 283.3899

ACTION – An inhibitor of neutrophil chemotaxis and degranulation induced by IL-8, as demonstrated *in vitro* by concentration-dependent inhibition of IL-8-induced chemotaxis of human polymorphonuclear (PMN) leukocytes in the concentration range from 0.01 nM to 1 μM, with potential in the treatment of neutrophil-dependent pathologies such as acute respiratory distress syndrome (ARDS), idiopathic fibrosis, ischemia and reperfusion damage, psoriasis, rheumatoid arthritis, ulcerative colitis and glomerulonephritis. Another compound from this series of *N*-(2-arylpropionyl)-sulfonamides is:



DF-1661 [289581]: C17 H17 N O4 S

SOURCE – Dompé.

REFERENCES

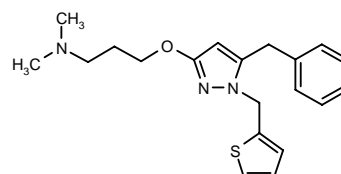
1. Bertini, R. et al. (Dompé Farmaceutici SpA) *N*-(2-Aryl-propionyl)-sulfonamides and pharmaceutical preparations containing them. WO 0024710.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

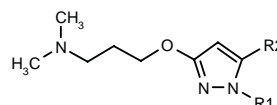
290191

N-[3-[5-Benzyl-1-(2-thienylmethyl)-1*H*-pyrazol-3-yloxy]-propyl]-*N,N*-dimethylamine

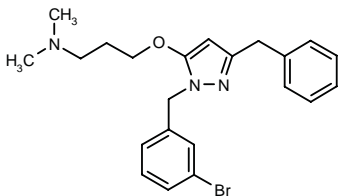


C20 H25 N3 O S; Mol wt: 355.5035

ACTION – Soluble guanylate cyclase (sGC) activator with vasodilating and platelet aggregation-inhibitory activity, potentially useful for the treatment or prevention of peripheral vascular diseases such as hypertension, angina pectoris and arteriosclerosis, as well as for the treatment or prevention of glaucoma, preeclampsia, Raynaud's syndrome, stroke and erectile dysfunction. *In vitro*, compound produced potent stimulation of recombinant sGC at a concentration of 1 μM and inhibited collagen-induced aggregation of human platelet-rich plasma with an IC₅₀ value of 0.5 μM. Other exemplified compounds from this series of pyrazole and indazole derivatives include the following:



Compound	R1	R2	Formula
290193	Ph	Ph	C ₂₀ H ₂₃ N ₃ O
290194	3,4-(Cl)2-PhCH ₂	CH ₂ Ph	C ₂₂ H ₂₅ Cl ₂ N ₃ O
290195	3-Br-PhCH ₂	CH ₂ Ph	C ₂₂ H ₂₆ BrN ₃ O
290196	2-Cl-PhCH ₂	CH ₂ Ph	C ₂₂ H ₂₆ ClN ₃ O

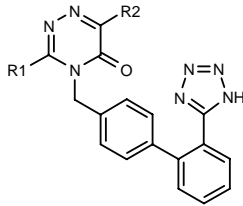


290363: C22 H26 Br N3 O

SOURCE – University College London, London (GB).

REFERENCES

1. Selwood, D. et al. (University College London) *Activators of soluble guanylate cyclase*. WO 0027394.



Compound	R1	R2	Formula
290215	Ph	Me	C ₂₄ H ₁₉ N ₇ O
290220	Ph	Ph	C ₂₉ H ₂₁ N ₇ O
290224	Bu	Me	C ₂₂ H ₂₃ N ₇ O
290227	Bu	Ph	C ₂₇ H ₂₅ N ₇ O

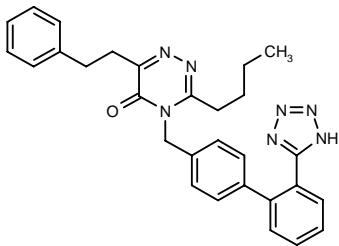
SOURCE – Development Center for Biotechnology, Taipei (TW).

REFERENCES

1. Yang, P.-H. et al. (Development Center for Biotechnology) *Angiotensin II receptor antagonistic 1,2,4-triazin-5-one derivs*. US 6071913.

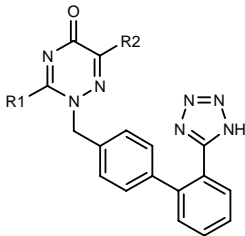
290211

3-Butyl-6-(2-phenylethyl)-4-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,2,4-triazin-5(4*H*)-one



C29 H29 N7 O; Mol wt: 491.5961

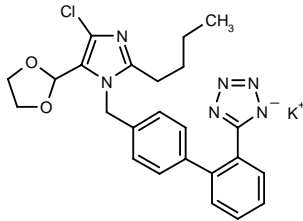
ACTION – Angiotensin II (All) AT₁ receptor antagonist (IC₅₀ = 55.1 nM) with potential in the treatment of cardiovascular diseases, particularly hypertension and congestive heart failure. Other specifically claimed compounds from this series of 1,2,4-triazin-5-one derivatives are:



Compound	R1	R2	Formula
290213	Ph	Me	C ₂₄ H ₁₉ N ₇ O
290219	Ph	Ph	C ₂₉ H ₂₁ N ₇ O
290222	Ph	CH ₂ CH ₂ Ph	C ₃₁ H ₂₅ N ₇ O
290223	Bu	Me	C ₂₂ H ₂₃ N ₇ O
290225	Bu	Ph	C ₂₇ H ₂₅ N ₇ O
290229	Bu	CH ₂ Ph	C ₂₈ H ₂₇ N ₇ O
290230	Bu	CH ₂ CH ₂ Ph	C ₂₉ H ₂₉ N ₇ O

290474

5-[4'-[2-Butyl-4-chloro-5-(1,3-dioxolan-2-yl)-1*H*-imidazol-1-ylmethyl]biphenyl-2-yl]-1*H*-tetrazole potassium salt



C24 H24 Cl K N6 O2; Mol wt: 503.0446

ACTION – Angiotensin II antagonist proven to exhibit superior antihypertensive properties to losartan in furosemide-treated conscious rats following oral administration, producing 17.3 and 25.38% reductions in blood pressure at 3 and 10 mg/kg p.o., respectively, vs. 11.7 and 21.8% reductions, respectively, for losartan at the same doses. In addition, it was more potent than losartan in inhibiting furosemide- and angiotensin II-induced hyperdipsia in rats (ID₂₅ = 1.86 mg/kg p.o. vs. 14.2 mg/kg p.o. for losartan) and exhibited a similar antihypertensive profile to losartan in renal hypertensive rats following oral administration. A representative compound from a series of 2-alkyl-5-halo-3-[2'-(tetrazol-5-yl)biphenyl-4-ylmethyl]-3*H*-imidazole-4-carboxaldehyde acetal derivatives.

SOURCE – Ferrer.

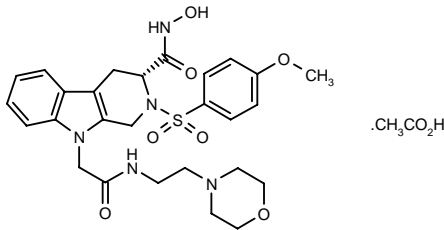
REFERENCES

1. Foguet, R. et al. (Ferrer Internacional SA) *2-Alkyl-5-halo-3-[2'-(tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazole-4-carboxaldehyde acetal derivs., their preparation and use*. WO 0031071.

TREATMENT OF DISORDERS OF
THE CORONARY ARTERIES
AND ATHEROSCLEROSIS

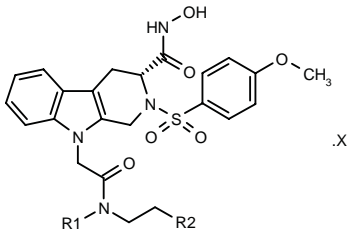
289843

2-(4-Methoxyphenylsulfonyl)-9-[2-[2-(4-morpholinyl)-ethylamino]-2-oxoethyl]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3(*R*)-carbohydroxamic acid acetate

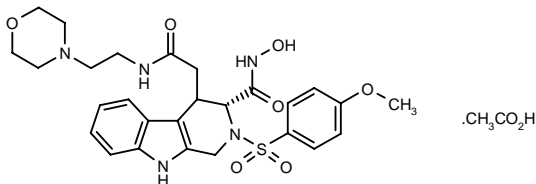


C27 H33 N5 O7 S . C2 H4 O2; Mol wt: 631.7033

ACTION – Matrix metalloproteinase inhibitor giving an IC₅₀ value of 32.6 nM for inhibition of fibroblast collagenase (MMP-1) and shown to suppress by 50-100% collagen-induced neovascularization in rat thoracic aorta at 1 μM. Potentially useful for the treatment of rheumatoid arthritis, arthrosis, cancer and atherosclerosis. Other specifically claimed pyrido[3,4-*b*]indole derivatives are:



Compound	R1	R2	X	Formula
289845	H	4-morpholinyl-CH2CH2S	HCl	C ₂₉ H ₃₇ N ₅ O ₇ S ₂ ·HCl
289846	H	4-morpholinyl-CH2CH2S		C ₂₉ H ₃₇ N ₅ O ₇ S ₂
289847	H	4-morpholinyl-CH2CH2SCH2	HCl	C ₃₀ H ₃₉ N ₅ O ₇ S ₂ ·HCl
289848	H	4-morpholinyl-CH2CH2SCH2		C ₃₀ H ₃₉ N ₅ O ₇ S ₂
289849	Me	4-morpholinyl	HCl	C ₂₈ H ₃₅ N ₅ O ₇ S·HCl
289850	Me	4-morpholinyl		C ₂₈ H ₃₅ N ₅ O ₇ S



289844: C27 H33 N5 O7 S . C2 H4 O2

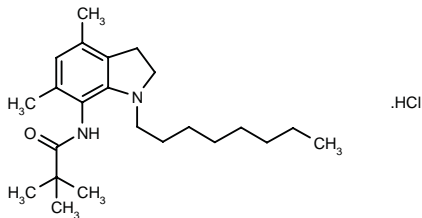
SOURCE – ADIR.

REFERENCES

1. De Nanteuil, G. et al. (ADIR et Cie.) *Metalloproteinase inhibitors*. EP 0916671, FR 2771095, US 6066633.

290157

N-(4,6-Dimethyl-1-octyl-2,3-dihydro-1*H*-indol-7-yl)-2,2-dimethylpropionamide hydrochloride



C23 H38 N2 O . HCl; Mol wt: 395.0271

ACTION – Orally bioavailable ACAT inhibitor with lipid peroxidation-inhibitory activity and therefore potentially useful for the treatment of atherosclerosis and hyperlipidemia. It inhibited ACAT from rabbit intestinal mucosal microsomes with an IC₅₀ of 0.09 μM and lipid peroxidation of rat brain homogenates by 97.9% at 10 μM. A comparable reduction in serum cholesterol levels was seen in hyperlipidemic rats (10 mg/kg/day in the diet) and normolipidemic hamsters (20 mg/kg/day in the diet) administered title compound (59.5 and 38.8%, respectively) and YM-750 (46.4 and 36.1%, respectively). Moreover, it exhibited an inhibitory effect on rabbit LDL oxidation similar to probucol (50.0 and 49.2%, respectively, at 5 μM). Concentrations effective against hepatic ACAT and LDL peroxidation were attained in plasma of dogs following an oral dose of 10 mg/kg.

SOURCE – Kyoto Pharmaceutical.

REFERENCES

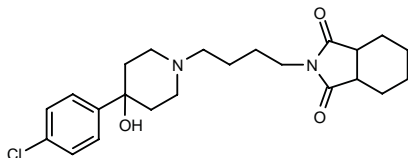
1. Matsui, H. et al. (Kyoto Pharmaceutical Industries, Ltd.) *Novel heterocyclic derivs., process for producing the same, and medicinal use thereof*. EP 0782986, JP 1996092210, US 5990150, WO 9609287.

2. Kamiya, S. et al. *Bioavailable acyl-CoA:cholesterol acyltransferase inhibitor with anti-peroxidative activity: Synthesis and biological activity of novel indolyl amide and urea derivatives*. Chem Pharm Bull 2000, 48(6): 817.

ST-6

290155

2-[4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]butyl]-perhydroisoindole-1,3-dione



C23 H31 Cl N2 O3; Mol wt: 418.9619

ACTION – Cardioprotective agent able to enhance posthypoxic contractile recovery of the hypoxic/reoxygenated rat heart (55% recovery of contractile force at 100 μg/min) *in vitro*. The compound appears to act by preventing sodium overload during oxygen deficiency.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Takeo, S. and Antoku, F. (Sumitomo Pharmaceuticals Co., Ltd.) *Myocardial protective agents*. JP 1992308569.

2. Takeo, S. et al. *The effects of a novel cyclohexane dicarboximide derivative, ST-6, on hypoxia/reoxygenation injury in perfused rat heart*. Biol Pharm Bull 2000, 23(6): 712.

TANGO-136

289834

ACTION – Transmembrane protein that exhibits homology with LRP-3 and is believed to be a member of the LDL receptor family and is thus considered to play a role in disorders of lipoprotein metabolism and transport, e.g., cardiovascular diseases such as atherosclerosis. Also disclosed are nucleic acids encoding the murine and human polypeptide, as well as antisense nucleic acid molecules, recombinant expression vectors, host cells and antibodies.

SOURCE – Millennium.

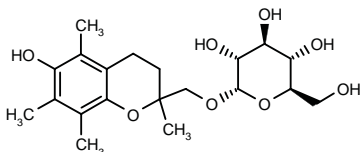
REFERENCES

1. McCarthy, S.A. (Millennium Pharmaceuticals, Inc.) *LDL related protein and uses thereof*. WO 0026227.

TMG

287213

2-(α -D-Glucopyranosyloxymethyl)-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-6-ol



C₂₀ H₃₀ O₈; Mol wt: 398.4490

ACTION – Highly water-soluble vitamin E derivative proven to inhibit free radical- and metal ion-induced lipid peroxidation. Compound (10 μ M) exhibited a protective effect against heart injury in a myocardial ischemia/reperfusion model *in vitro*, administered both pre- and postischemia. In the same model, compound also appeared to be able to scavenge reactive oxygen species, in particular H₂O₂. Potentially useful for the treatment of cancer and heart disease involving oxidation processes mediated by free radicals.

SOURCES – CCI Corporation; Kyoto Prefectural University of Medicine, Kyoto (JP).

REFERENCES

1. Kunieda, T. and Murase, H. (CCI Corporation) *Preparation method of glycoside using immobilized enzyme*. JP 1997313196.

2. Murase, H. et al. (CCI Corporation) *Chromanol glycoside and method for production thereof*. US 5478812.

3. Murase, H. et al. (CCI Corporation) *Preventive and therapeutic agent for ophthalmopathy*. JP 1999343241.

4. Murase, H. et al. (CCI Corporation) *Preventive and therapeutic agents for systemic inflammatory reaction syndrome*. JP 2000154154.

5. Tachiana, G. et al. (CCI Corporation) *Radioprotective agents*. JP 1998072356.

6. Yoshida, N. et al. (CCI Corporation) *Prophylactic and therapeutic agent for inflammatory intestinal diseases*. EP 0965344, WO 9825629.

7. Yoshikawa, T. et al. (CCI Corporation) *Preventives and remedies for ischemic reflow disorder*. WO 9939719.

8. Murase, H. et al. *Antioxidant activity of a novel vitamin E derivative, 2-(α -D-glucopyranosyl)methyl-2,5,7,8-tetramethylchroman-6-ol*. Free Radical Biol Med 1998, 24(2): 217.

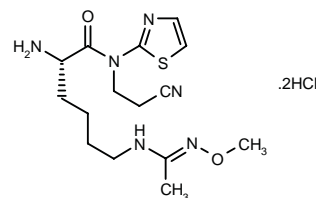
9. Murase, H. et al. *Synthesis of a novel vitamin E derivative, 2-(α -D-glucopyranosyl)methyl-2,5,7,8-tetramethylchroman-6-ol, by α -glucosidase-catalyzed transglycosylation*. Lipids 1997, 32(1): 73.

10. Okabe, E. et al. *Protective effect of TMG, a novel vitamin E derivative, on myocardial ischemia-reperfusion injury*. Jpn J Pharmacol 2000, 82(Suppl. 1): Abst O-305.

TREATMENT OF SHOCK

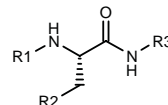
289891

N-(2-Cyanoethyl)-N-(2-thiazolyl)-N^ε-[1-(methoxyimino)ethyl]-L-lysine dihydrochloride

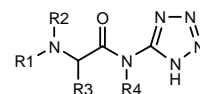


C₁₅ H₂₄ N₆ O₂ S . 2HCl; Mol wt: 425.3824

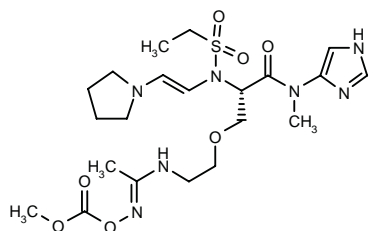
ACTION – Nitric oxide synthase (NOS) inhibitor that exhibits selective inhibition or modulation of the inducible over the constitutive NOS isoforms. Other specifically claimed amino acid heterocyclic amide derivatives include the following:



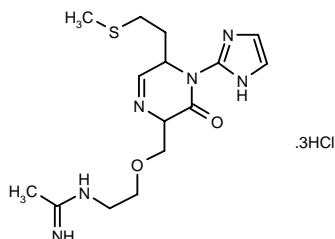
Compound	R1	R2	R3	Formula
289892	H	SCH ₂ CH ₂ NHC(=NH)Me	4-Pyr-N(Ac)	C ₁₄ H ₂₁ N ₅ O ₂ S
289894	SO ₂ Me	2-[MeC(=NOH)NHCH ₂]-Ph	2-oxo-3-THF-NH	C ₁₇ H ₂₄ N ₄ O ₆ S



Compound	R1	R2	R3	R4	Formula
289893	OH	Ac	(CH ₂) ₄ NHC(=NH)Me	OH	C ₁₁ H ₂₀ N ₄ O ₄
289898	H	H	(S)-CH ₂ SCH ₂ CH ₂ N(OH)-C(Me)=NCH ₂ OCH ₂ Ph	Me	C ₁₇ H ₂₆ N ₄ O ₃ S
289899	H	H-L-Phe-	(S)-(CH ₂) ₄ NH-C(=NH)CH ₂ F	Me	C ₁₉ H ₂₆ FN ₄ O ₂



289895: C21 H35 N7 O7 S



289897: C15 H24 N6 O2 S . 3HCl

SOURCE – Pharmacia.

REFERENCES

1. Hansen, D.W. Jr. et al. (G.D. Searle & Co.) *Novel amino acid heterocyclic amide derivs. useful as nitric oxide synthase inhibitors*. WO 0026195.

TREATMENT OF PERIPHERAL VASCULAR DISEASE

ONO-1608¹⁻⁴

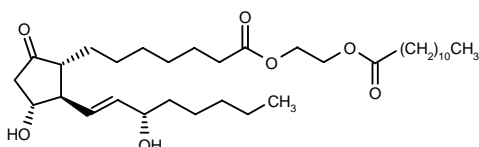
275114

Liposomal formulation of egg lecithin and Ono-PM-123

ONO-PM-123^{*,1,2}

248568

Prostaglandin E₁ 2-(dodecanoyloxy)ethyl ester



C34 H60 O7; Mol wt: 580.8530

ACTION – Liposomal formulation of the prostaglandin E₁ prodrug Ono-PM-123 and egg lecithin proven to induce a sustained increase in blood flow and skin temperature in peripheral sites in rats, as well as to improve intermittent claudication, skin ulcers and tail gangrene in rat peripheral artery occlusion models. In addition, compound inhibited neointimal thickening in a vascular balloon injury model in baboons. Potentially useful for the treatment of peripheral arterial occlusive diseases (PAOD) such as intermittent claudication and skin ulcer.

SOURCE – Ono.

REFERENCES

1. Nishiura, A. et al. (Ono Pharmaceutical Co., Ltd.) *Prostaglandin derivs*. EP 0758645, JP 1997110828, US 5690957.

2. Murakata, S. et al. *ONO-1608: A liposomal formulation of prostaglandin E1 (PGE1) prodrug*. 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 50.

3. *1999 annual report reflects progress in clinical trials at Ono*. DailyDrugNews.com (Daily Essentials) 1999, Oct 28.

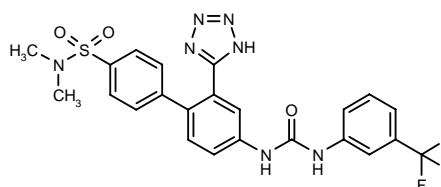
4. *Ono: Annual Report 1998*. DailyDrugNews.com (Daily Essentials) 1998, Nov 12.

*Identified compound **248568** (see **248096**) Drug Data Rep1997, 019(05): 0424.

MISCELLANEOUS CARDIOVASCULAR DRUGS

289550

N-[4'-(*N,N*-Dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-*N'*-[3-(trifluoromethyl)phenyl]urea



C23 H20 F3 N7 O3 S; Mol wt: 531.5170

ACTION – Potent chloride channel blocker proven active in both normal and sickle cell erythrocytes, giving a K_d value of 0.3 μM. It is expected to be of use for the treatment of sickle cell anemia, brain edema following ischemia or tumors, diarrhea, hypertension, bone metabolic disorders, osteoclast-associated disorders and glaucoma.

SOURCE – NeuroSearch.

REFERENCES

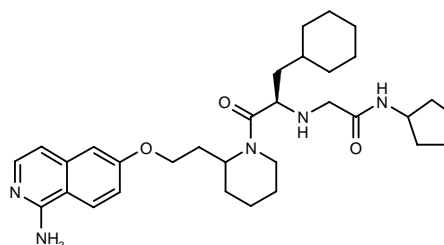
1. Dahl, B.H. and Christophersen, P. (NeuroSearch A/S) *Substd. phenyl derivs., their preparation and use*. WO 0024707.

AGENTS AFFECTING BLOOD COAGULATION

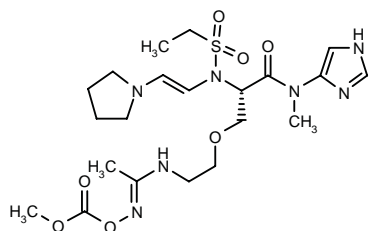
ANTICOAGULANTS

289617

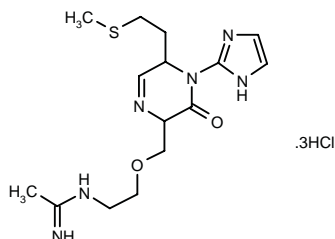
2-[2-[2-(1-Aminoisoquinolin-6-yloxy)ethyl]piperidin-1-yl]-1(*R*)-(cyclohexylmethyl)-2-oxoethylamino]-*N*-cyclopentylacetamide



C32 H47 N5 O3; Mol wt: 549.7553



289895: C21 H35 N7 O7 S



289897: C15 H24 N6 O2 S . 3HCl

SOURCE – Pharmacia.

REFERENCES

1. Hansen, D.W. Jr. et al. (G.D. Searle & Co.) *Novel amino acid heterocyclic amide derivs. useful as nitric oxide synthase inhibitors*. WO 0026195.

TREATMENT OF PERIPHERAL VASCULAR DISEASE

ONO-1608¹⁻⁴

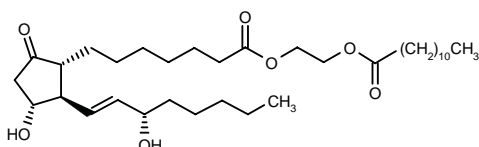
275114

Liposomal formulation of egg lecithin and Ono-PM-123

ONO-PM-123^{*,1,2}

248568

Prostaglandin E₁ 2-(dodecanoyloxy)ethyl ester



C34 H60 O7; Mol wt: 580.8530

ACTION – Liposomal formulation of the prostaglandin E₁ prodrug Ono-PM-123 and egg lecithin proven to induce a sustained increase in blood flow and skin temperature in peripheral sites in rats, as well as to improve intermittent claudication, skin ulcers and tail gangrene in rat peripheral artery occlusion models. In addition, compound inhibited neointimal thickening in a vascular balloon injury model in baboons. Potentially useful for the treatment of peripheral arterial occlusive diseases (PAOD) such as intermittent claudication and skin ulcer.

SOURCE – Ono.

REFERENCES

1. Nishiura, A. et al. (Ono Pharmaceutical Co., Ltd.) *Prostaglandin derivs*. EP 0758645, JP 1997110828, US 5690957.

2. Murakata, S. et al. *ONO-1608: A liposomal formulation of prostaglandin E1 (PGE1) prodrug*. 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 50.

3. *1999 annual report reflects progress in clinical trials at Ono*. DailyDrugNews.com (Daily Essentials) 1999, Oct 28.

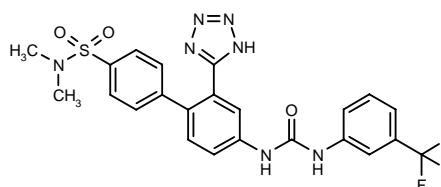
4. *Ono: Annual Report 1998*. DailyDrugNews.com (Daily Essentials) 1998, Nov 12.

*Identified compound **248568** (see **248096**) Drug Data Rep1997, 019(05): 0424.

MISCELLANEOUS CARDIOVASCULAR DRUGS

289550

N-[4'-(*N,N*-Dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-*N*'-[3-(trifluoromethyl)phenyl]urea



C23 H20 F3 N7 O3 S; Mol wt: 531.5170

ACTION – Potent chloride channel blocker proven active in both normal and sickle cell erythrocytes, giving a K_d value of 0.3 μM. It is expected to be of use for the treatment of sickle cell anemia, brain edema following ischemia or tumors, diarrhea, hypertension, bone metabolic disorders, osteoclast-associated disorders and glaucoma.

SOURCE – NeuroSearch.

REFERENCES

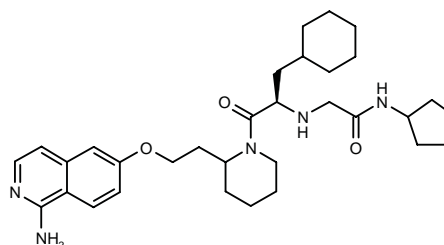
1. Dahl, B.H. and Christophersen, P. (NeuroSearch A/S) *Substd. phenyl derivs., their preparation and use*. WO 0024707.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

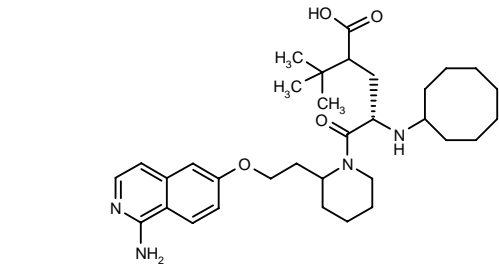
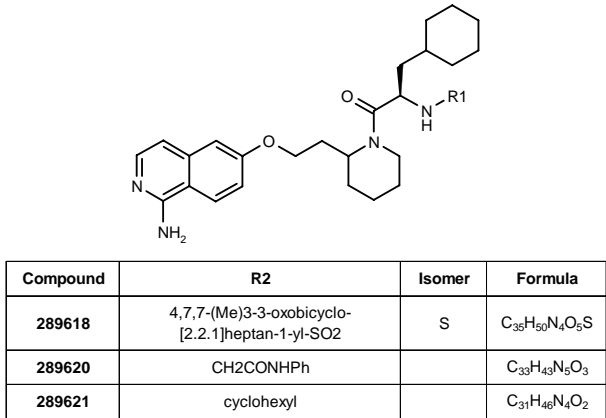
289617

2-[2-[2-(1-Aminoisoquinolin-6-yloxy)ethyl]piperidin-1-yl]-1(*R*)-(cyclohexylmethyl)-2-oxoethylamino]-*N*-cyclopentylacetamide



C32 H47 N5 O3; Mol wt: 549.7553

ACTION – Serine protease inhibitor, particularly active against thrombin ($IC_{50} = 0.32 \mu M$), potentially useful as an anticoagulant. Other exemplified compounds include the following:



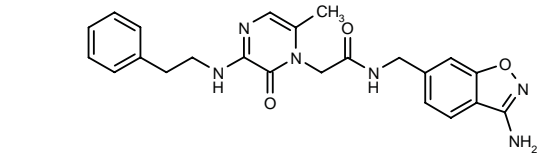
SOURCE – Akzo Nobel.

REFERENCES

1. Timmers, C.M. and Rewinkel, J.B.A. (Akzo Nobel N.V.) *Serine protease inhibitor*. WO 0024718.

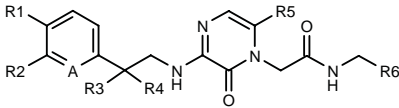
289808

N-(3-Amino-1,2-benzisoxazol-6-ylmethyl)-2-[6-methyl-2-oxo-3-(2-phenylethylamino)-1,2-dihydropyrazin-1-yl]acetamide



C₂₃ H₂₄ N₆ O₃; Mol wt: 432.4816

ACTION – Thrombin inhibitor ($K_i < 100 \text{ nM}$) for the treatment of thrombotic conditions such as angina, myocardial infraction, ischemia, atrial fibrillation, stroke and deep vein thrombosis. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	R5	R6	A	Formula
289809	H	H	H	H	Me	3-NH2-1H-pyrazolo-[3,4-b]pyridin-6-yl	CH	C ₂₂ H ₂₄ N ₈ O ₂
289811	H	H	H	H	Me	3-NH2-6-indazolyl	CH	C ₂₃ H ₂₅ N ₇ O ₂
289813	H	H	H	H	Me	6-indolyl	CH	C ₂₄ H ₂₅ N ₅ O ₂
289814	H	H	H	H	Me	1-Me-6-indazolyl	N	C ₂₃ H ₂₅ N ₇ O ₂
289816	-OCH2O-		H	H	Me	1-Me-6-indazolyl	CH	C ₂₅ H ₂₆ N ₆ O ₄
289817	H	H	H	H	Me	6-indazolyl	CH	C ₂₃ H ₂₄ N ₆ O ₂
289818	H	H	H	H	Me	1H-pyrrolo-[3,2-c]pyridin-6-yl	CH	C ₂₃ H ₂₄ N ₆ O ₂
289819	H	H	F	F	Cl	3-NH2-6-benzisoxazolyl	CH	C ₂₂ H ₁₉ ClF ₂ N ₆ O ₃

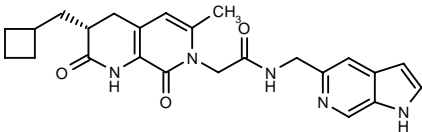
SOURCE – Merck & Co.

REFERENCES

1. Sanderson, P.E. et al. (Merck & Co., Inc.) *Thrombin inhibitors*. WO 0026210.

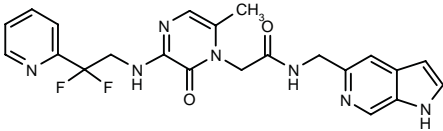
289820

2-[3(*R*)-(Cyclobutylmethyl)-6-methyl-2,8-dioxo-1,2,3,4,7,8-hexahydro[1,7]naphthyridin-7-yl]-*N*-(1*H*-pyrrolo[2,3-*c*]pyridin-5-ylmethyl)acetamide



C₂₄ H₂₇ N₅ O₃; Mol wt: 433.5093

ACTION – Thrombin inhibitor ($K_i < 20 \text{ nM}$) for the treatment of thrombotic conditions such as angina, myocardial infarction, ischemia, atrial fibrillation, stroke and deep vein thrombosis. Another specifically claimed compound is:



289821: C₂₂ H₂₁ F₂ N₇ O₂

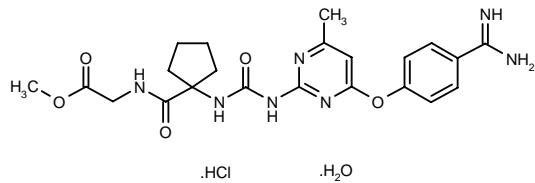
SOURCE – Merck & Co.

REFERENCES

1. Sanderson, P.E. et al. (Merck & Co., Inc.) *Thrombin inhibitors*. WO 0026211.

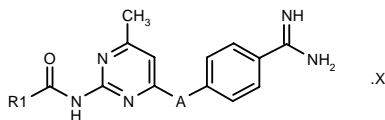
290109

2-[1-[3-[4-(4-Amidinophenoxy)-6-methylpyrimidin-2-yl]ureido]cyclopentylcarboxamido]acetic acid methyl ester hydrochloride hydrate



C22 H27 N7 O5 . HCl . H2O; Mol wt: 523.9750

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of serine proteases such as thrombin, proven to prolong thrombin time (TT) with an ED₂₀₀ value (concentration doubling TT) of 0.05 μM. Other specifically claimed compounds within this series of pyrimidine derivatives are:



Compound	R1	A	X	Formula
290110	cyclopentyl	O		C ₁₈ H ₂₁ N ₅ O ₂
290111	cyclohexyl-NH	O	HCl.H2O	C ₁₉ H ₂₄ N ₅ O ₂ .HCl.H ₂ O
290112	NHC(Me)2Et	NH	HCl.H2O	C ₁₈ H ₂₅ N ₇ O.HCl.H ₂ O
290113	NHCH(i-Pr)CO2Et	O	HCl.H2O	C ₂₀ H ₂₆ N ₆ O ₄ .HCl.H ₂ O
290114	1-(MeOCOCH2NHCO)-cyclohexyl-NH	NH		C ₂₃ H ₃₀ N ₆ O ₄

SOURCE – Boehringer Ingelheim.

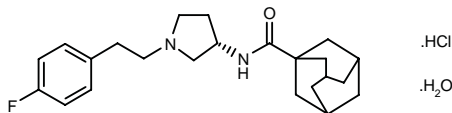
REFERENCES

1. Lehmann-Lintz, T. et al. (Boehringer Ingelheim Pharma KG) *Novel pyrimidines, the production thereof and their use.* DE 19851421, WO 0027826.

ANTIPLATELET THERAPY

289794

N-[1-[2-(4-Fluorophenyl)ethyl]pyrrolidin-3(S)-yl]adamantane-1-carboxamide hydrochloride hydrate



C23 H31 F N2 O . HCl . H2O; Mol wt: 424.9846

ACTION – Antiplatelet agent, a 5-HT₂ receptor antagonist (IC₅₀ = 0.18 nM for inhibition of [³H]-ketanserin binding in rat cerebral cortex membranes vs. 27 nM for sarpogrelate) proven to inhibit collagen-induced aggregation of rabbit platelet-rich plasma with an IC₅₀ of 1.9 nM versus 260 nM for sarpogrelate. In addition, compound was shown to be more effective than sarpogrelate and cilostazol when tested in rat models of intermittent claudication induced by femoral artery ligation and lauric acid-induced peripheral artery obstruction at a dose of 10 or 30 mg/kg p.o. vs. 100 mg/kg p.o. for sarpogrelate and cilostazol, while it did not induce any significant changes in heart rate or blood pressure at doses up to 100 mg/kg p.o. in rats, contrary to cilostazol. Potentially useful for improving peripheral circulation, treating thromboembolic disorders and promoting lacrimal secretion. A representative compound from a series of pyrrolidine derivatives.

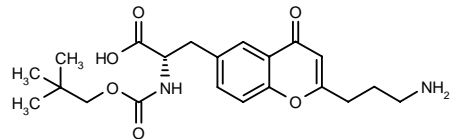
SOURCE – Welfide.

REFERENCES

1. Kuroita, T. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Pyrrolidine cpds. and medicinal utilization thereof.* WO 0026186.

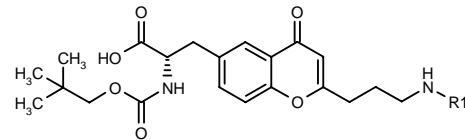
289799

3-[2-(3-Aminopropyl)-4-oxo-4H-1-benzopyran-6-yl]-2(S)-(2,2-dimethylpropoxycarboxamido)propionic acid

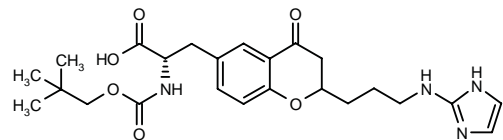


C21 H28 N2 O6; Mol wt: 404.4602

ACTION – Integrin inhibitor that acts by inhibiting the binding of fibrinogen to the human α_vβ₃ receptor and is thus expected to be of use in the treatment of thrombosis, myocardial infarction, coronary heart diseases, arteriosclerosis, cancer, osteoporosis and rheumatoid arthritis. Other specifically claimed compounds from this series of chromenone and chromanone derivatives are:



Compound	R1	Formula
289800	2-imidazolyl	C ₂₄ H ₃₀ N ₄ O ₆
289803	2-Pyr	C ₂₆ H ₃₁ N ₃ O ₆
289804	2-benzimidazolyl	C ₂₈ H ₃₂ N ₄ O ₆



289802: C24 H32 N4 O6

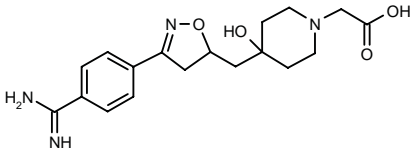
SOURCE – Merck KGaA.

REFERENCES

1. Fittschen, C. et al. (Merck Patent GmbH) *Chromenone and chromanone derivs. as integrin inhibitors*. DE 19850131, WO 0026212.

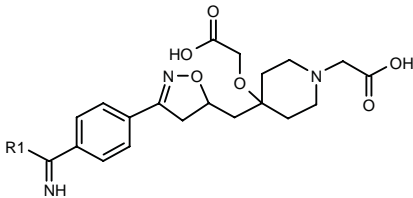
290419

2-[4-[3-(4-Amidinophenyl)-4,5-dihydroisoxazol-5-ylmethyl]-4-hydroxypiperidin-1-yl]acetic acid

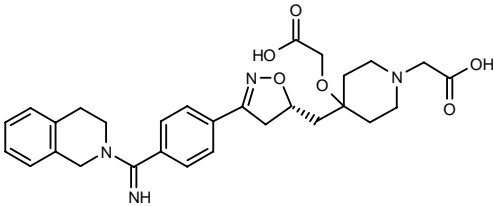


C18 H24 N4 O4; Mol wt: 360.4116

ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIIb/IIIa) receptor antagonist. Other exemplified compounds from this series of isoxazoline and isoxazole derivatives include the following:



Compound	R1	Formula
290420	NH2	C ₂₀ H ₂₆ N ₄ O ₆
290421	4-morpholinyl	C ₂₄ H ₃₂ N ₄ O ₇
290422	NHBu	C ₂₄ H ₃₄ N ₄ O ₆
290423	2,6-(Me)2-4-morpholinyl	C ₂₆ H ₃₆ N ₄ O ₇
290424	4-Me-1-Piz	C ₂₅ H ₃₅ N ₅ O ₆
290425	1-Pip	C ₂₅ H ₃₄ N ₄ O ₆
290426	4-Ph-1-Piz	C ₃₀ H ₃₇ N ₅ O ₆
290427	4-thiomorpholinyl	C ₂₄ H ₃₂ N ₄ O ₆ S



290429: C29 H34 N4 O6

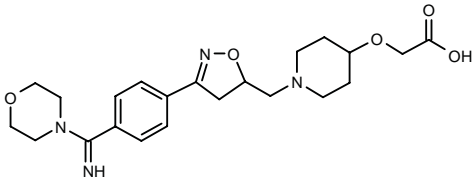
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Smallheer, J.M. et al. (DuPont Pharmaceuticals Co.) *Novel isoxazoline fibrinogen receptor antagonists*. WO 0029406.

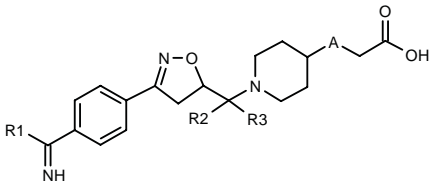
290432

2-[1-[3-[4-[Imino(4-morpholinyl)methyl]phenyl]-4,5-dihydroisoxazol-5-ylmethyl]piperidin-4-yloxy]acetic acid



C22 H30 N4 O5; Mol wt: 430.5020

ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIIb/IIIa) receptor antagonist. Other exemplified compounds from this series of isoxazoline derivatives include the following:



Compound	R1	R2	R3	A	Formula
290436	4-Me-1-Piz	H	H	O	C ₂₃ H ₃₃ N ₅ O ₄
290438	NHBu	H	H	O	C ₂₂ H ₃₂ N ₄ O ₄
290439	NH2	H	H	bond	C ₁₈ H ₂₄ N ₄ O ₃
290441	NHBu	H	H	bond	C ₂₂ H ₃₂ N ₄ O ₃
290442	4-morpholinyl	H	H	bond	C ₂₂ H ₃₀ N ₄ O ₄
290443	NHBu	-O-		bond	C ₂₂ H ₃₀ N ₄ O ₄

SOURCE – DuPont Pharmaceuticals.

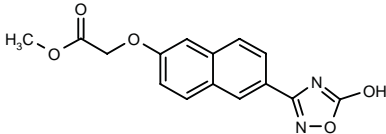
REFERENCES

1. Wityak, J. and Jadhav, P.K. (DuPont Pharmaceuticals Co.) *Isoxazoline fibrinogen receptor antagonists*. WO 0029407.

THROMBOLYTICS

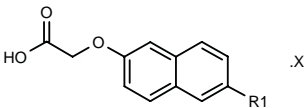
290590

2-[6-(5-Hydroxy-1,2,4-oxadiazol-3-yl)naphthalen-2-yloxy]-acetic acid methyl ester



C15 H12 N2 O5; Mol wt: 300.2688

ACTION – Antithrombotic and thrombolytic agent with excellent fibrinolysis-accelerating effects. *In vitro*, compound exhibited plasmin formation-promoting activity, while *in vivo* it was found to protect against thrombin-induced thrombosis in mice following oral and intravenous administration, survival rates being 55% when given at 1 mg/kg p.o. and 80% when given at 0.1 mg/kg i.v. Other compounds from this series of naphthalene derivatives include the following:



Compound	R1	X	Formula
290591	2-Pyr		C ₁₇ H ₁₃ NO ₃
290592	4,5-dihydro-2-oxazolyl	HCl	C ₁₅ H ₁₃ NO ₄ ·HCl

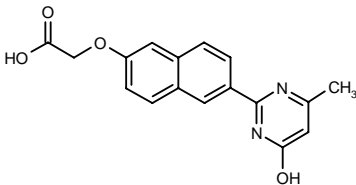
SOURCE – Torii.

REFERENCES

1. Ashizawa, H. et al. (Torii Pharmaceutical Co., Ltd.) *Novel naphthalene derivs.* WO 0031036.

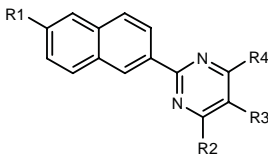
290593

2-[6-(4-Hydroxy-6-methylpyrimidin-2-yl)naphthalen-2-yloxy]acetic acid



C17 H14 N2 O4; Mol wt: 310.3076

ACTION – Antithrombotic and thrombolytic agent with excellent fibrinolysis-accelerating effects. *In vitro*, compound exhibited plasmin formation-promoting activity, while *in vivo* it was found to protect against thrombin-induced thrombosis in mice following oral and intravenous administration, survival rates being 70% when given at 1 mg/kg p.o. and 80% when given at 0.1 mg/kg i.v. Other compounds from this series of naphthalene derivatives include the following:



Compound	R1	R2	R3	R4	Formula
290594	O(CH2)3CO2H	OH	H	Me	C ₁₉ H ₁₈ N ₂ O ₄
290595	CONHCH2CH2N(Me)2	Cl	H	Me	C ₂₀ H ₂₁ ClN ₄ O
290596	OMe	OMe	CO2H	H	C ₁₇ H ₁₄ N ₂ O ₄

SOURCE – Torii.

REFERENCES

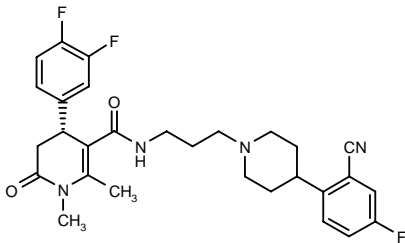
1. Ashizawa, H. et al. (Torii Pharmaceutical Co., Ltd.) *Naphthalene derivs.* WO 0031045.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

289762

N-[3-[4-(2-Cyano-4-fluorophenyl)-1-piperidinyl]propyl]-4(*R*)-(3,4-difluorophenyl)-1,2-dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide



C29 H31 F3 N4 O2; Mol wt: 524.5839

ACTION – α_{1A} -Adrenoceptor antagonist with a K_i value of < 50 nM in an α_{1A} -adrenoceptor binding assay and about 40-fold more selective for this receptor than for α_{1B} - and α_{1D} -adrenoceptors. The compound is potentially useful for the treatment of benign prostatic hyperplasia with reduced side effects related to peripheral adrenergic blockade such as hypotension, syncope, lethargy, etc.

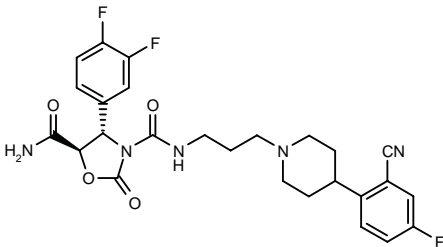
SOURCES – Merck & Co.; Synaptic.

REFERENCES

1. Barrow, J. et al. (Merck & Co., Inc.) *Dihydropyridinones and pyrrolinones useful as α_{1a} -adrenoceptor antagonists.* WO 0025782.
2. Nantermet, P.G. et al. *Selective α_{1a} adrenergic antagonists based on 4-aryl-3,4-dihydropyridine-2-ones.* Bioorg Med Chem Lett 2000, 10(15): 1625.

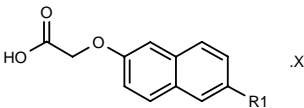
289951

N³-[3-[4-(2-Cyano-4-fluorophenyl)-1-piperidinyl]propyl]-4(*S*)-(3,4-difluorophenyl)-2-oxooxazolidine-3,5(*R*)-dicarboxamide



C26 H26 F3 N5 O4; Mol wt: 529.5164

ACTION – Selective α_{1A} -adrenoceptor antagonist reported to have a K_i value of 1 nM or less in binding assays, being 100-fold more selective in binding to α_{1A} -adrenoceptors vs. α_{1B} - and α_{1D} -adrenoceptors. Potentially useful for the treatment of benign prostatic hyperplasia.



Compound	R1	X	Formula
290591	2-Pyr		C ₁₇ H ₁₃ NO ₃
290592	4,5-dihydro-2-oxazolyl	HCl	C ₁₅ H ₁₃ NO ₄ ·HCl

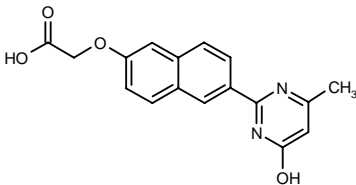
SOURCE – Torii.

REFERENCES

1. Ashizawa, H. et al. (Torii Pharmaceutical Co., Ltd.) *Novel naphthalene derivs.* WO 0031036.

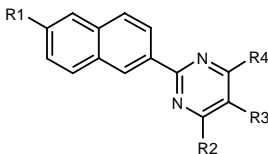
290593

2-[6-(4-Hydroxy-6-methylpyrimidin-2-yl)naphthalen-2-yloxy]acetic acid



C17 H14 N2 O4; Mol wt: 310.3076

ACTION – Antithrombotic and thrombolytic agent with excellent fibrinolysis-accelerating effects. *In vitro*, compound exhibited plasmin formation-promoting activity, while *in vivo* it was found to protect against thrombin-induced thrombosis in mice following oral and intravenous administration, survival rates being 70% when given at 1 mg/kg p.o. and 80% when given at 0.1 mg/kg i.v. Other compounds from this series of naphthalene derivatives include the following:



Compound	R1	R2	R3	R4	Formula
290594	O(CH2)3CO2H	OH	H	Me	C ₁₉ H ₁₈ N ₂ O ₄
290595	CONHCH2CH2N(Me)2	Cl	H	Me	C ₂₀ H ₂₁ ClN ₄ O
290596	OMe	OMe	CO2H	H	C ₁₇ H ₁₄ N ₂ O ₄

SOURCE – Torii.

REFERENCES

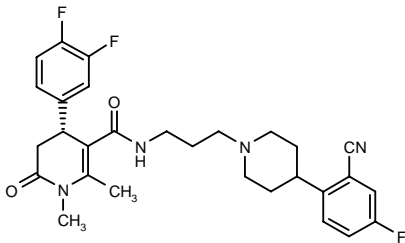
1. Ashizawa, H. et al. (Torii Pharmaceutical Co., Ltd.) *Naphthalene derivs.* WO 0031045.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

289762

N-[3-[4-(2-Cyano-4-fluorophenyl)-1-piperidinyl]propyl]-4(*R*)-(3,4-difluorophenyl)-1,2-dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide



C29 H31 F3 N4 O2; Mol wt: 524.5839

ACTION – α_{1A} -Adrenoceptor antagonist with a K_i value of < 50 nM in an α_{1A} -adrenoceptor binding assay and about 40-fold more selective for this receptor than for α_{1B} - and α_{1D} -adrenoceptors. The compound is potentially useful for the treatment of benign prostatic hyperplasia with reduced side effects related to peripheral adrenergic blockade such as hypotension, syncope, lethargy, etc.

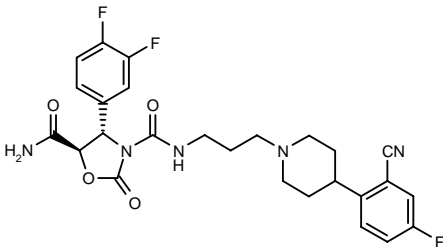
SOURCES – Merck & Co.; Synaptic.

REFERENCES

1. Barrow, J. et al. (Merck & Co., Inc.) *Dihydropyridinones and pyrrolinones useful as α_{1a} -adrenoceptor antagonists.* WO 0025782.
2. Nantermet, P.G. et al. *Selective α_{1a} adrenergic antagonists based on 4-aryl-3,4-dihydropyridine-2-ones.* Bioorg Med Chem Lett 2000, 10(15): 1625.

289951

*N*³-[3-[4-(2-Cyano-4-fluorophenyl)-1-piperidinyl]propyl]-4(*S*)-(3,4-difluorophenyl)-2-oxooxazolidine-3,5(*R*)-dicarboxamide



C26 H26 F3 N5 O4; Mol wt: 529.5164

ACTION – Selective α_{1A} -adrenoceptor antagonist reported to have a K_i value of 1 nM or less in binding assays, being 100-fold more selective in binding to α_{1A} -adrenoceptors vs. α_{1B} - and α_{1D} -adrenoceptors. Potentially useful for the treatment of benign prostatic hyperplasia.

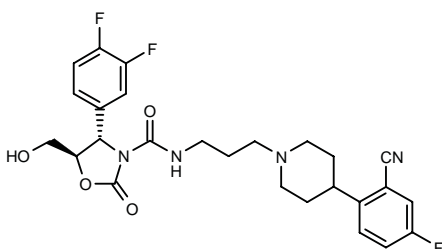
SOURCE – Merck & Co.

REFERENCES

1. Nerenberg, J.B. et al. (Merck & Co., Inc.) *Oxazolidinones useful as α_{1a} adrenoceptor antagonists*. WO 0027827.

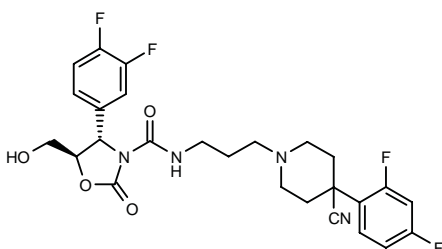
289952

N-[3-[4-(2-Cyano-4-fluorophenyl)-1-piperidiny]propyl]-4(*S*)-(3,4-difluorophenyl)-5(*R*)-(hydroxymethyl)-2-oxo-oxazolidine-3-carboxamide



C26 H27 F3 N4 O4; Mol wt: 516.5173

ACTION – Selective α_{1A} -adrenoceptor antagonist reported to have a K_i value of 1 nM or less in binding assays, being 500-fold more selective in binding to α_{1A} -adrenoceptors vs. α_{1B} - and α_{1D} -adrenoceptors. Potentially useful for the treatment of benign prostatic hyperplasia. Another specifically claimed oxazolidinone is:



289953: C26 H26 F4 N4 O4

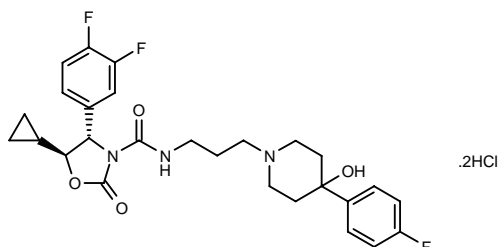
SOURCE – Merck & Co.

REFERENCES

1. Nerenberg, J.B. et al. (Merck & Co., Inc.) *Oxazolidinones useful as α_{1a} adrenoceptor antagonists*. WO 0027817.

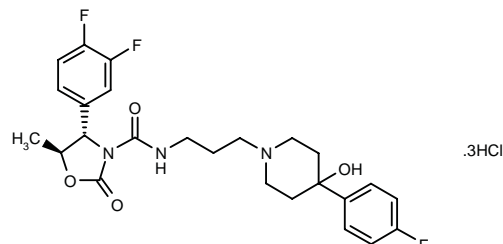
290132

(+)-5(*S*)-Cyclopropyl-4(*S*)-(3,4-difluorophenyl)-*N*-[3-[4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]propyl]-2-oxo-oxazolidine-3-carboxamide dihydrochloride



C27 H30 F3 N3 O4 . 2HCl; Mol wt: 590.4668

ACTION – Agent for the treatment of benign prostatic hyperplasia with potent α_{1A} -adrenoceptor-antagonist activity (K_i = 0.11 nM) and 1,918- and 3,218-fold selectivity over α_{1B} - and α_{1D} -adrenoceptors, respectively. Another specifically claimed compound from this series of oxazolidinone derivatives is:



290133: C25 H28 F3 N3 O4 . 3HCl

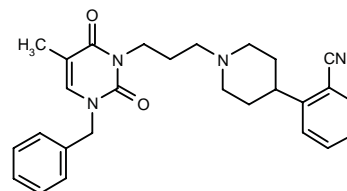
SOURCE – Merck & Co.

REFERENCES

1. Selnick, H.G. and Barrow, J. (Merck & Co., Inc.) *Oxazolidinones useful as α_{1a} adrenoceptor antagonists*. WO 0027816.

290335

2-[1-[3-(3-Benzyl-5-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-1-yl)propyl]piperidine-4-yl]benzonitrile



C27 H30 N4 O2; Mol wt: 442.5600

ACTION – Selective α_{1A} -adrenoceptor antagonist giving a K_i < 30 nM in a screening assay using membranes from cells stably transfected with the human receptor and > 10-fold more selective for α_{1A} - than for α_{1B} - and α_{1D} -adrenoceptors. Potentially useful for the treatment of benign prostatic hyperplasia. Other exemplified pyrimidinedione derivatives include the following:

SOURCE – Sanofi-Synthélabo.

REFERENCES

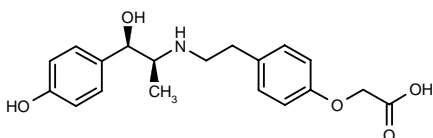
1. Philippo, C. et al. (Sanofi-Synthélabo) *1-Aminoethylquinoline derivs. for treating urinary incontinence*. FR 2785903, WO 0029379.

TREATMENT OF RENAL DISEASES

KUL-7211*

273733

(–)-2-[4-[2-[2(*R*)-Hydroxy-2-(4-hydroxyphenyl)-1(*S*)-methylethylamino]ethyl]phenoxy]acetic acid



C19 H23 N O5; Mol wt: 345.3927

ACTION – β_2/β_3 -Adrenoceptor agonist with selectivity relative to β_1 -adrenoceptors, as demonstrated in binding and functional assays. It blocked KCl-induced contractions in rabbit, dog and human ureter at concentrations of 1 nM to 100 μ M. *In vivo* in dogs with acute ureteral obstruction, both compound (3-30 μ g/kg i.v.) and isoproterenol (1-10 mg/kg i.v.) reduced elevated ureteral pressure, although the effect of title compound lasted much longer than that of isoproterenol, and both also attenuated weight gain and histological changes in the kidney and the interruption in urine flow. Compound exhibited less pronounced effects on hemodynamics than isoproterenol. Potentially useful for the treatment of ureteral colic and urolithiasis.

SOURCE – Kissei.

REFERENCES

1. Tamai, T. et al. (Kissei Pharmaceutical Co., Ltd.) *Aminoethylphenoxyacetic acid derivs. and drugs for pain remission and calculi removal promotion in urinary lithiasis*. EP 1002791, WO 9905090.

2. Murakami, M. et al. *Pharmacological profile of KUL-7211 - A specific β -adrenoceptor agonist for ureteral smooth muscle*. J Urol 2000, 163(4, Suppl.): Abst 373.

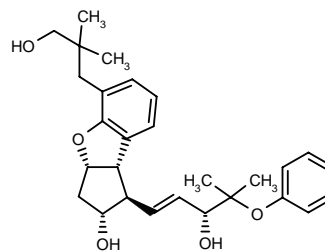
*Identified compound **273733** Drug Data Rep 1999, 021(04): 0328.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

289740

(1*R*,2*R*,3*aS*,8*bS*)-5-(3-Hydroxy-2,2-dimethylpropyl)-1-[3(*R*)-hydroxy-4-methyl-4-phenoxy-1(*E*)-pentenyl]-2,3,3*a*,8*b*-tetrahydro-1*H*-cyclopenta[*b*][1]benzofuran-2-ol



C28 H36 O5; Mol wt: 452.5874

ACTION – Anti-*Helicobacter pylori* agent, a representative compound from a series of 5,6,7-trinor-4,8-*inter-m*-phenylene PGI₂ derivatives. The compound gave MIC values of 75-124 μ M against several *H. pylori* strains.

Other compounds of the invention are reported to induce platelet aggregation or cervical ripening.

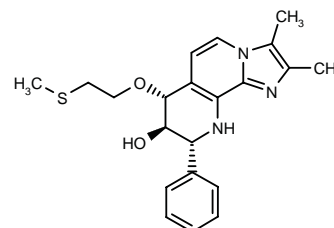
SOURCE – Toray.

REFERENCES

1. Wakita, H. et al. (Toray Industries, Inc.) *5,6,7-Trinor-4,8-inter-m-phenylene PGI₂ deriv. and drugs containing the same*. WO 0024727.

289763

2,3-Dimethyl-7(*R*)-[2-(methylsulfonyl)ethoxy]-9(*R*)-phenyl-7,8,9,10-tetrahydroimidazo[1,2-*h*][1,7]naphthyridin-8(*R*)-ol



C21 H25 N3 O2 S; Mol wt: 383.5135

ACTION – Gastric antisecretory agent able to produce 100% inhibition of pentagastrin-stimulated gastric acid secretion in perfused rat stomach *in vivo* at 3 μ mol/kg i.v. Potentially useful for the treatment of gastrointestinal inflammatory diseases and lesions, e.g., gastric and duodenal ulcer, gastritis, dyspepsia, etc. Another exemplified imidazonaphthyridine is:

SOURCE – Sanofi-Synthélabo.

REFERENCES

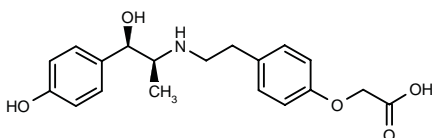
1. Philippo, C. et al. (Sanofi-Synthélabo) *1-Aminoethylquinoline derivs. for treating urinary incontinence*. FR 2785903, WO 0029379.

TREATMENT OF RENAL DISEASES

KUL-7211*

273733

(–)-2-[4-[2-[2(*R*)-Hydroxy-2-(4-hydroxyphenyl)-1(*S*)-methylethylamino]ethyl]phenoxy]acetic acid



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ACTION – β_2/β_3 -Adrenoceptor agonist with selectivity relative to β_1 -adrenoceptors, as demonstrated in binding and functional assays. It blocked KCl-induced contractions in rabbit, dog and human ureter at concentrations of 1 nM to 100 μ M. *In vivo* in dogs with acute ureteral obstruction, both compound (3-30 μ g/kg i.v.) and isoproterenol (1-10 mg/kg i.v.) reduced elevated ureteral pressure, although the effect of title compound lasted much longer than that of isoproterenol, and both also attenuated weight gain and histological changes in the kidney and the interruption in urine flow. Compound exhibited less pronounced effects on hemodynamics than isoproterenol. Potentially useful for the treatment of ureteral colic and urolithiasis.

SOURCE – Kissei.

REFERENCES

1. Tamai, T. et al. (Kissei Pharmaceutical Co., Ltd.) *Aminoethylphenoxyacetic acid derivs. and drugs for pain remission and calculi removal promotion in urinary lithiasis*. EP 1002791, WO 9905090.

2. Murakami, M. et al. *Pharmacological profile of KUL-7211 - A specific β -adrenoceptor agonist for ureteral smooth muscle*. J Urol 2000, 163(4, Suppl.): Abst 373.

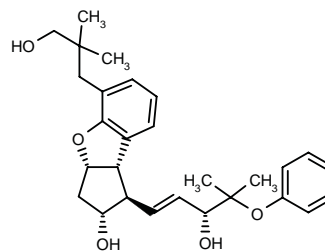
*Identified compound **273733** Drug Data Rep 1999, 021(04): 0328.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

289740

(1*R*,2*R*,3*aS*,8*bS*)-5-(3-Hydroxy-2,2-dimethylpropyl)-1-[3(*R*)-hydroxy-4-methyl-4-phenoxy-1(*E*)-pentenyl]-2,3,3*a*,8*b*-tetrahydro-1*H*-cyclopenta[*b*][1]benzofuran-2-ol



C28 H36 O5; Mol wt: 452.5874

ACTION – Anti-*Helicobacter pylori* agent, a representative compound from a series of 5,6,7-trinor-4,8-*inter-m*-phenylene PGI₂ derivatives. The compound gave MIC values of 75-124 μ M against several *H. pylori* strains.

Other compounds of the invention are reported to induce platelet aggregation or cervical ripening.

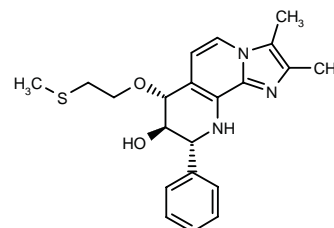
SOURCE – Toray.

REFERENCES

1. Wakita, H. et al. (Toray Industries, Inc.) *5,6,7-Trinor-4,8-inter-m-phenylene PGI₂ deriv. and drugs containing the same*. WO 0024727.

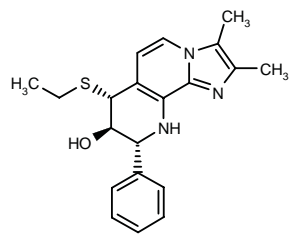
289763

2,3-Dimethyl-7(*R*)-[2-(methylsulfonyl)ethoxy]-9(*R*)-phenyl-7,8,9,10-tetrahydroimidazo[1,2-*h*][1,7]naphthyridin-8(*R*)-ol



C21 H25 N3 O2 S; Mol wt: 383.5135

ACTION – Gastric antisecretory agent able to produce 100% inhibition of pentagastrin-stimulated gastric acid secretion in perfused rat stomach *in vivo* at 3 μ mol/kg i.v. Potentially useful for the treatment of gastrointestinal inflammatory diseases and lesions, e.g., gastric and duodenal ulcer, gastritis, dyspepsia, etc. Another exemplified imidazonaphthyridine is:



289764: C20 H23 N3 O S

SOURCE – Byk Gulden.

REFERENCES

1. Grundler, G. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Imidazonaphthyridines*. WO 0026217.

289995

L-Valyl-L-valyl-L-lysyl-L-lysyl-L-alanyl-L-asparaginy-L-glutamyl-glycyl-L-leucyl-L-threonyl-L-tryptophyl-L-asparaginy-L-seryl-L-leucyl-L-lysyl-L-aspartyl-L-lysyl-L-lysyl-L-seryl-L-cysteinyl-L-histidyl-L-threonyl-L-alanyl-L-valyl-L-aspartyl-L-arginyl-L-threonyl-L-alanyl-glycyl-L-tryptophyl-L-asparaginy-L-isoleucyl-L-proline

C161 H260 N48 O48 S; Mol wt: 3668.1790

ACTION – Peptide isolated from a lactoferrin hydrolysate that inhibits the adhesion of *Helicobacter pylori* to mucosal surfaces and is therefore potentially useful for treating or preventing gastrointestinal disorders caused by this pathogen such as gastritis, gastric ulcer and duodenal ulcer.

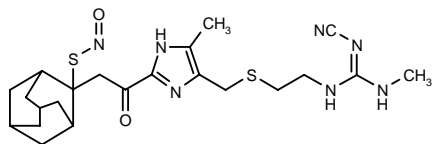
SOURCE – Meiji Milk Products.

REFERENCES

1. Mukai, T. et al. (Meiji Milk Products Co., Ltd.) *Cell adhesion inhibitors*. JP 2000136148.

290276

(Z)-N²-Cyano-N¹-methyl-N³-[2-[5-methyl-2-[2-[2-(nitrososulfanyl)adamantan-2-yl]acetyl]-1 H-imidazol-4-ylmethylsulfanyl]ethyl]guanidine



C22 H31 N7 O2 S2; Mol wt: 489.6659

ACTION – A representative compound from a series of nitrosated and nitrosylated histamine H₂ receptor antagonists that exhibits improved gastroprotective properties as compared to H₂ receptor antagonists, as demonstrated *in vivo* by significant inhibition of ethanol/HCl-induced gastric lesions in rats at 160 and 320 µg/kg p.o., whereas the parent drug cimetidine at the same doses failed to significantly inhibit the formation of gastric lesions. Potentially useful for the treatment or prevention of gastrointestinal disorders, for decreasing the recurrence of ulcers, for facilitating ulcer healing, for the treatment or prevention of inflammation, microbial

infections, ophthalmic diseases, multiple sclerosis and viral infections, and for reducing the gastrointestinal toxicity associated with the use of NSAIDs.

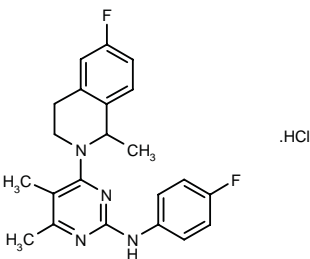
SOURCE – NitroMed.

REFERENCES

1. Garvey, D.S. et al. (NitroMed Inc.) *Nitrosated and nitrosylated H2 receptor antagonist cpds., compsns. and methods of use*. WO 0028988.

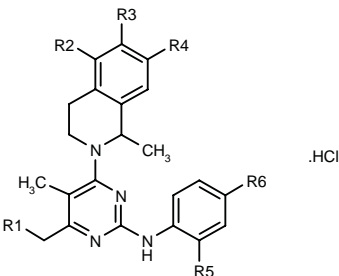
290404

N-[4-(6-Fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-5,6-dimethylpyrimidin-2-yl]-N-(4-fluorophenyl)amine hydrochloride



C22 H22 F2 N4 . HCl; Mol wt: 416.9007

ACTION – Proton pump inhibitor with improved efficacy as a gastric actisecretory agent. It was more potent than omeprazole in inhibiting H⁺/K⁺-ATPase *in vitro* (IC₅₀ = 0.7 µM vs. 11.5 µM for omeprazole) and *in vivo* in inhibiting gastric acid secretion in pylorus-ligated rats. Other exemplified pyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
290406	H	H	H	F	H	F	C ₂₂ H ₂₂ F ₂ N ₄ .HCl
290408	H	H	H	F	H	H	C ₂₂ H ₂₃ FN ₄ .HCl
290409	H	H	H	F	Me	F	C ₂₃ H ₂₄ F ₂ N ₄ .HCl
290410	H	H	F	H	H	H	C ₂₂ H ₂₃ FN ₄ .HCl
290411	H	H	F	H	Me	H	C ₂₃ H ₂₅ FN ₄ .HCl
290414	F	H	H	H	H	F	C ₂₂ H ₂₂ F ₂ N ₄ .HCl
290415	H	H	H	Cl	H	F	C ₂₂ H ₂₂ ClFN ₄ .HCl
290416	H	Cl	H	H	Me	H	C ₂₃ H ₂₅ ClN ₄ .HCl

SOURCE – Yuhan.

REFERENCES

1. Lee, J.W. et al. (Yuhan Corp.) *Novel pyrimidine derivs. and processes for the preparation thereof*. WO 0029403.

DOSMALFATE⁺

Rec INN; USAN

162108

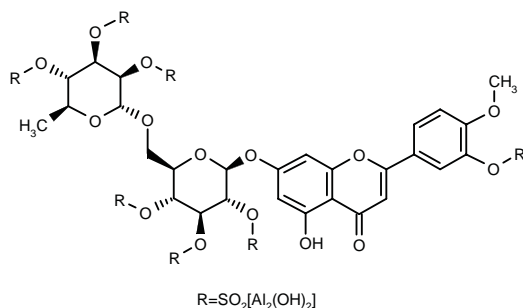
[μ_7 -[7-[[6-*O*-(6-Deoxy-2,3,4-tri-*O*-sulfo- α -L-mannopyranosyl)-2,3,4-tri-*O*-sulfo- β -D-glucopyranosyl]oxy]-5-hydroxy-2-[4-methoxy-3-(sulfooxy)phenyl]-4*H*-1-benzopyran-4-onato(7-)]tetradeca- μ -hydroxyheneicosahydroxytetradecaaluminum

[μ_7 -[[Diosmin heptasulfato](7-)]tetracontahydroxytetradecaaluminum

F-3616

F-3616M

Flavalfate



C28 H60 Al14 O71 S7 ; Mol wt: 2134.9210

ACTION – Cytoprotective agent.

INDICATION – Prevention and treatment of gastroduodenal lesions induced by chronic treatment with NSAID therapy.

PRESENTATION – Ampules, 1500 mg; suspension, 1500 mg/10 ml; and dispersable tablets, 1500 mg.

PROPRIETARY NAME – *Diotul* (ES).**SOURCE** – FAES.**REFERENCES**

- Orjales-Venero, A. and Mosquera-Pestana, R. (FAES) *Sulfated diosmin deriv.* EP 0558435, ES 2041216, JP 1994008677, US 5296469.
- Arteche, J.K. et al. *Toxicology and pharmacokinetics of dosmalfate.* Drugs Today 2000, 36(Suppl. A): 55.
- Cohen de Lara, A. et al. *Two comparative studies of dosmalfate vs. misoprostol in the prevention of NSAID-induced gastric ulcers in rheumatic patients.* Drugs Today 2000, 36(Suppl. A): 73.
- Corcóstegui, R. et al. *Gastroprotective action of dosmalfate.* Drugs Today 2000, 36(Suppl. A): 25.
- Labeaga, L. and Orjales, A. *Pharmacological profile of dosmalfate.* Drugs Today 2000, 36(Suppl. A): 59.
- Labeaga, L. et al. *Effect of dosmalfate on several experimental gastric mucosal damages in the rat.* 14th Int Symp Med Chem (Sept 8-12, Maastricht) 1996, Abst P-3.15.
- Lanas, A. *Gastric cytoprotection: Current concepts.* Drugs Today 2000, 36(Suppl. A): 1.
- Le Kerneau, J. et al. *A comparative study of the gastroprotective action of three doses of dosmalfate vs. placebo in the prevention of acute aspirin-induced gastric lesions.* Drugs Today 2000, 36(Suppl. A): 67.
- Ucelay, M. et al. *Preclinical safety profile of dosmalfate.* Drugs Today 2000, 36(Suppl. A): 41.
- Dosmalfate launched in Spain for prophylaxis of gastric lesions and ulcers.* DailyDrugNews.com (Daily Essentials) 2000, June 1.

11. *Proposed international nonproprietary names (Prop. INN): List 62.* WHO Drug Inf 1989, 3(4): 212.

12. Dosmalfate Collaborative Group. *Two comparative studies of dosmalfate vs. sucralfate in the healing of peptic ulcers.* Drugs Today 2000, 36(Suppl. A): 79.

13. FAES SA Company Communication 1995, May 12.

14. FAES SA Company Communication 2000, March 29.

MONOGRAPH – Orjales, A. *Dosmalfate.* Drugs Fut 1999, 24(4): 0381.

*Drug Data Rep 1996, 018(03): 0249.

HP0310**290897**

Protein from Helicobacter pylori strain NCTC 11637 with a molecular weight of 35 kD

ACTION – Antigenic protein derived from *Helicobacter pylori* and found to protect mice against *H. pylori* infection, potentially useful as a prophylactic vaccine.

SOURCE – Provalis.**REFERENCES**

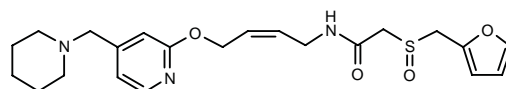
- Dunkley, M. and Harris, S. (Provalis Ltd.) *Helicobacter pylori antigen.* WO 0029432.

LAFUTIDINE

Rec INN

145925

(\pm)-2-(Furfurylsulfinyl)-*N*-[4-[4-(piperidin-1-ylmethyl)-pyridin-2-yloxy]-2(*Z*)butenyl]acetamide

FRG-8813⁺

C22 H29 N3 O4 S; Mol wt: 431.5541

ACTION – Histamine H₂ receptor antagonist.**INDICATION** – Treatment of gastric ulcers.**PRESENTATION** – Tablets, 5 and 10 mg.

PROPRIETARY NAMES AND MANUFACTURERS – *Stogar* (UCB Japan; JP); *Protecadin* (Taiho; JP).

RECENT REFERENCES

- Hirakawa, N. et al. *A novel histamine 2(H2) receptor antagonist with gastroprotective activity. II. Synthesis and pharmacological evaluation of 2-furfuryl-thio and 2-furfurylsulfinyl acetamide derivatives with heteroaromatic rings.* Chem Pharm Bull 1998, 46(4): 616.
- Kato, S. et al. *Protective effect of lafutidine against indomethacin-induced intestinal ulceration in rats: Relation to capsaicin-sensitive sensory neurons.* Digestion 2000, 61(1): 39.
- Mizoguchi, H. et al. *Effect of lafutidine, a histamine H2-receptor antagonist, on indomethacin-induced small intestinal lesions in rats: Role of capsaicin-sensitive neurons (CSN).* Jpn J Pharmacol 2000, 82(Suppl. 1): Abst P-537.
- Onodera, S. et al. *Antilucer effect of lafutidine on indomethacin-induced gastric antral ulcers in refed rats.* Jpn J Pharmacol 1999, 80(3): 229.
- Onodera, S. et al. *Effect of lafutidine, a novel antiulcer agent, on healing and relapse of acetic acid-induced gastric ulcer in rats.* Folia Pharmacol Jpn 1998, 111(3): 167.

6. Onodera, S. et al. *Gastroprotective mechanism of lafutidine, a novel anti-ulcer drug with histamine H₂-receptor antagonistic activity*. *Arzneim-Forsch Drug Res* 1999, 49(6): 519.

7. Sato, N. et al. *The novel histamine H₂ receptor antagonist FRG-8813 prevents delay of wound repair induced by hydrogen peroxide in a rabbit gastric epithelial cell system*. *J Gastroenterol Hepatol* 1998, 13(Suppl. 2): S209.

8. Tashima, K. et al. *Effects of lafutidine, a novel histamine H₂-receptor antagonist, on gastrointestinal lesions in rats: Relation to capsaicin sensitive sensory neurons*. *Dig Dis Week* (May 17-20, New Orleans) 1998, Abst 342.

9. Umeda, M. et al. *Effect of lafutidine, a novel histamine H₂-receptor antagonist, on monochloramine-induced gastric lesions in rats: Role of capsaicin-sensitive sensory neurons*. *J Gastroenterol Hepatol* 1999, 14(9): 859.

10. *May launch announced for UCB H₂ receptor antagonist*. *DailyDrugNews.com* (Daily Essentials) 2000, June 30.

11. *Salix negotiates lafutidine license agreement with Fujirebio*. *DailyDrugNews.com* (Daily Essentials) 1999, Feb 18.

MONOGRAPH – Prous, J. et al. *Lafutidine*. *Drugs Fut* 1994, 19(9): 0835.

*Drug Data Rep 1989, 011(01): 0031.

INFLAMMATORY BOWEL DISEASE THERAPY

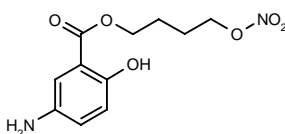
NCX-456

291410

5-Amino-2-hydroxybenzoic acid 4-(nitrooxy)butyl ester

NO-Mesalamine

NO-5-ASA



C11 H14 N2 O6; Mol wt: 270.2396

ACTION – Nitric oxide (NO)-releasing derivative of mesalamine with improved antiinflammatory activity in a rat model of colitis. In this model, compound reduced colonic damage and granulocyte infiltration of the colon, as well as inhibiting chemotaxin-induced leukocyte adherence to vascular endothelium, more effectively than mesalamine. It suppressed lipopolysaccharide- and concanavalin A-induced IL-1 β and interferon gamma release from isolated rat splenocytes and inhibited caspase 1 activity. Potentially useful as a treatment for inflammatory bowel disease.

SOURCE – NicOx.

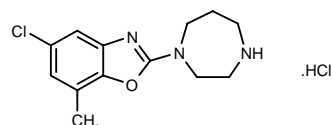
REFERENCES

1. Del Soldato, P. (NicOx SA) *Medicine nitrate salts*. WO 0006585.
2. Fiorucci, S. et al. *NO-mesalamine (NCX-456) inhibits effector caspases and protects colonic epithelial cells from cytokine induced apoptosis*. *Gastroenterology* 2000, 118(4, Suppl. 2, Part 1): A872.
3. Wallace, J.L. et al. *Enhanced anti-inflammatory effects of a nitric oxide-releasing derivative of mesalamine in rats*. *Gastroenterology* 1999, 117(3): 557.

ANTIDIARRHEAL AGENTS

290561

5-Chloro-2-(perhydro-1,4-diazepin-1-yl)-7-methylbenzoxazole hydrochloride



C13 H16 Cl N3 O . HCl; Mol wt: 302.2033

ACTION – Agent for the treatment or prevention of diarrhea, gastrointestinal motility disorders and irritable bowel syndrome with 5-HT₃ receptor-antagonist activity. *In vivo*, compound inhibited restraint stress-induced diarrhea in rats with an ED₅₀ value of 0.00025 mg/kg p.o. compared to an ED₅₀ value of 0.025 mg/kg p.o. for granisetron, and it dose-dependently increased colonic transit time in mice following oral administration. No mortality was observed following administration of 300 mg/kg p.o. to mice. A representative compound from a series of benzoxazole derivatives.

SOURCE – Meiji Seika.

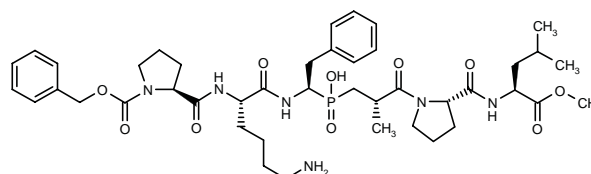
REFERENCES

1. Shiokawa, S. et al. (Meiji Seika Kaisha, Ltd.) *Benzoxazole derivs. and drugs containing the same as the active ingredient*. WO 0031073.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

290125

N-[3-[1(*R*)]-(*N*-Benzyloxycarbonyl-L-prolyl-L-lysylamino)-2-phenylethyl(hydroxy)phosphoryl]-2(*S*)-methylpropionyl]-L-prolyl-L-leucine methyl ester



C43 H63 N6 O10 P; Mol wt: 854.9767

ACTION – Agent for the treatment of fibrotic disorders, particularly liver fibrosis, a selective procollagen C-proteinase (PCP, procollagen C-endopeptidase) inhibitor. *In vitro*, compound was shown to almost completely inhibit recombinant PCP activity at a concentration of 100 nM.

SOURCE – Bayer.

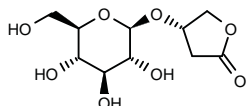
REFERENCES

1. Burchardt, E.-R. et al. (Bayer AG) *Phosphinate peptide analogs for the treatment of fibrotic disorders*. DE 19850072, WO 0027377.

GOODYEROSIDE A

290156

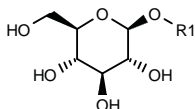
4(*S*)-(β-D-Glucopyranosyloxy)tetrahydrofuran-2-one



C₁₀ H₁₆ O₈; Mol wt: 264.2284

Colorless needles, *m.p.* 156-7 °C; $[\alpha]_D^{25}$ -71.2 ° (*c* 0.55, H₂O).

ACTION – Hepatoprotective agent, an aliphatic glycoside produced by *Goodyera* spp. It suppressed elevated lactate dehydrogenase (LDH), glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) levels in CCl₄-treated primary cultured rat hepatocytes at concentrations of 0.1-10.0 µg/ml. Other constituents of these plants are:



Compound	R1	Formula
290159	(<i>S</i>)-CH(HOCH ₂)CH ₂ CO ₂ H	C ₁₀ H ₁₈ O ₉
290412	2-oxo-4(<i>R</i>)-THF	C ₁₀ H ₁₆ O ₈
290413	(<i>R</i>)-CH(HOCH ₂)CH ₂ CO ₂ H	C ₁₀ H ₁₈ O ₉

SOURCES – Kyushu University, Fukuoka-shi (JP); Seiwa Pharmaceuticals.

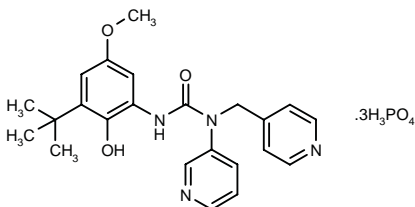
REFERENCES

1. Du, X.-M. et al. *Hepatoprotective aliphatic glycosides from three Goodyera species*. Biol Pharm Bull 2000, 23(6): 731.

T-0970

290960

N'-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-*N*-(3-pyridyl)-*N*-(4-pyridylmethyl)urea triphosphate



C₂₃ H₂₆ N₄ O₃ . 3 H₃ O₄ P; Mol wt: 700.4645

ACTION – Antioxidant, a ureidophenol derivative proven to inhibit spontaneous lipid peroxidation in rat brain with a potency about 10 times greater than that of α-tocopherol, probucol and butylhydroxytoluene (IC₅₀ = 0.30, 3.81, 4.06 and 3.8 µM, respectively). Compound also exhibited superoxide anion- and hydroxyl radical-scavenging activity *in vitro*. *In vivo*, it exerted a protective effect against hepatic injury, as demonstrated in the ferric nitrilotriacetate-induced tissue injury model in rats, where it dose-dependently (3-10 mg/kg p.o.) depressed increased GOT and GTP levels.

SOURCE – Tanabe Seiyaku.

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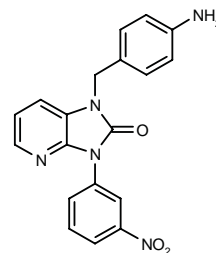
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ZNC-2381*

283679

1-(4-Aminobenzyl)-3-(3-nitrophenyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one



C₁₉ H₁₅ N₅ O₃; Mol wt: 361.3595

ACTION – Hepatoprotectant proven to protect mice against hepatic injury induced by D-galactosamine/lipopolysaccharide, *Propionibacterium* acnes/lipopolysaccharide or concanavalin A at oral doses of 3-30 mg/kg. In these animals, treatment with compound significantly reduced the serum levels of alanine aminotransferase, liver DNA fragmentation and DNA-ladder formation, as well as hepatocellular necrosis induced by treatment with the hepatotoxic substances. In addition, at doses of 1-30 mg/kg, it dose-dependently suppressed concanavalin A-induced increases in serum levels of TNF-α, interferon gamma and IL-2, and inhibited TNF-α mRNA expression in the liver.

SOURCES – Nippon Chemiphar; Zeria.

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*Identified compound **283679** (see **283676**) Drug Data Rep 2000, 022(02): 0154.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

(FMS)₃-INSULIN

291316

1A-[N-(2-Sulfo-9H-fluoren-9-ylmethoxycarbonyl)glycine]-1B-[N-(2-sulfo-9H-fluoren-9-ylmethoxycarbonyl)-L-phenylalanine]-29B-[N⁶-(2-sulfo-9H-fluoren-9-ylmethoxy-carbonyl)-L-lysine]-insulin (human)

ACTION – Water-soluble, long-acting insulin prodrug able to lower circulating glucose levels for a prolonged period ($t_{1/2}$ = 30 h) when given to diabetic streptozotocin-treated rats as a single s.c. dose of 3 mg/kg. When administered i.p. to healthy rats, it also lowered blood glucose levels and showed a longer half-life than native and NPH-insulin ($t_{1/2}$ = 14, 8 and 10 h, respectively). Upon incubation at pH 7.4 and 37 °C, compound underwent slow hydrolysis with linear regeneration of insulin possessing full biological activity. Potentially useful for the treatment of type 1 diabetes.

SOURCES – Weizmann Institute of Science, Rehovot (IL); Yeda.

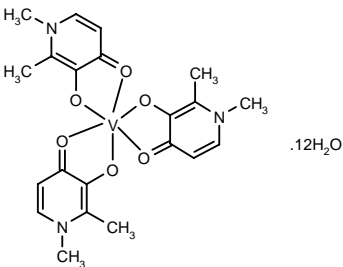
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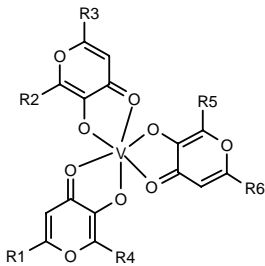
289603

Tris[3-(hydroxy-κO)-1,2-dimethylpyridin-4(1H)-onato-κO⁴]vanadium dodecahydrate

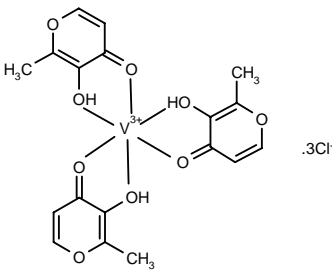


C21 H24 N3 O6 V . 12H2O; Mol wt: 681.5552

ACTION – Organic complex of vanadium(III) with glucose-lowering activity in streptozotocin-diabetic rats, potentially useful for the treatment of hyperglycemic and proliferative disorders. Other exemplified complexes are:



Compound	R1	R2	R3	R4	R5	R6	Formula
289604	H	Me	H	Me	Me	H	C ₁₈ H ₁₅ O ₉ V
289605	H	Et	H	Et	Et	H	C ₂₁ H ₂₁ O ₉ V
289606	CH2OH	H	CH2OH	H	H	CH2OH	C ₁₈ H ₁₅ O ₁₂ V



289608: C18 H18 Cl3 O9 V

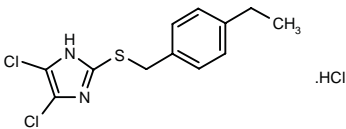
SOURCE – University of British Columbia, Vancouver, BC (CA).

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1. Orvig, C. et al. (University of British Columbia) *Organic vanadium(III) complexes and their use*. WO 0024730.

289646

4,5-Dichloro-2-(4-ethylbenzylsulfanyl)-1H-imidazole hydrochloride



C12 H12 Cl2 N2 S . HCl; Mol wt: 323.6737

ACTION – Agent for the treatment of insulin resistance and diabetes proven to significantly reduce blood glucose and cholesterol levels in non-insulin-dependent diabetic KKA^y mice at 1200 mg/kg/day p.o. x 5 days. In addition, compound was shown to inhibit arachidonic-acid induced rabbit platelet aggregation (100% inhibition at 30 μM), as well as to inhibit cyclooxygenase type 1 (77% inhibition at 300 μM) and 5-lipoxygenase (97% inhibition at 30 μM). A representative compound from a series of imidazole derivatives.

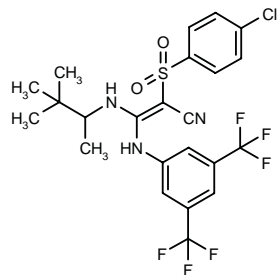
SOURCE – Sumitomo Pharmaceuticals.

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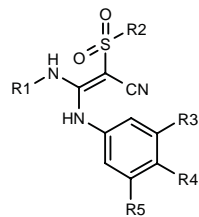
290010

3-[3,5-Bis(trifluoromethyl)phenylamino]-2-(4-chloro-phenylsulfonyl)-3-(1,2,2-trimethylpropylamino)-2(*E*)-propenenitrile



C23 H22 Cl F6 N3 O2 S; Mol wt: 553.9528

ACTION – ATP-sensitive potassium (K_{ATP}) channel opener for the treatment of endocrinological disorders, particularly hyperinsulinemia and diabetes. Other specifically claimed substituted 3,3-diamino-2-propenenitriles include the following:



Compound	R1	R2	R3	R4	R5	Formula
290011	t-BuCH(Me)	4-Cl-Ph	OMe	H	OMe	C ₂₃ H ₂₆ ClN ₃ O ₄ S
290012	(S)-t-BuCH(Me)	4-Cl-Ph	CF ₃	H	CF ₃	C ₂₃ H ₂₂ ClF ₆ N ₃ O ₂ S
290013	C(Me)2Et	4-Cl-Ph	OMe	H	OMe	C ₂₂ H ₂₆ ClN ₃ O ₄ S
290014	t-BuCH(Me)	Me	F	H	CF ₃	C ₁₇ H ₂₁ F ₄ N ₃ O ₂ S
290015	cyclopentyl	i-Pr	CF ₃	H	CF ₃	C ₁₉ H ₂₁ F ₆ N ₃ O ₂ S
290016	C(Me)2Et	Me	H	-OCH ₂ O-		C ₁₆ H ₂₁ N ₃ O ₄ S

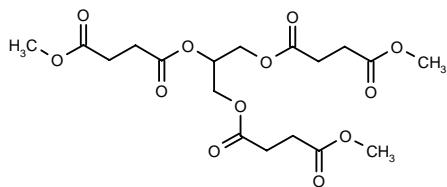
SOURCE – Novo Nordisk.

REFERENCES

1. Hansen, J.B. et al. (Novo Nordisk A/S) *Substd. 3,3-diamino-2-propenenitriles, their preparation and use.* WO 0027805.

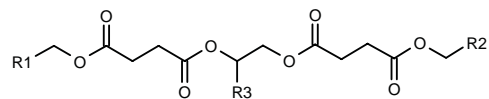
290198

4,4',4''-(Propane-1,2,3-triyl)trioxytris(4-oxobutyric acid methyl ester)

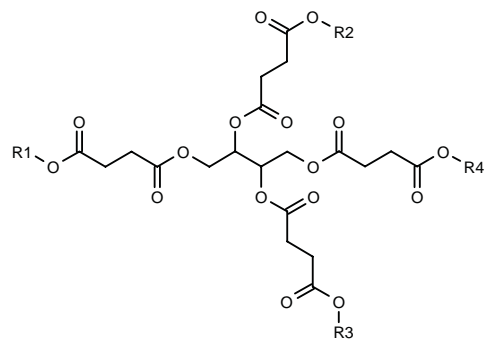


C18 H26 O12; Mol wt: 434.3914

ACTION – Agent for the treatment of metabolic diseases including diabetes, acute starvation, endotoxemia, sepsis, systemic inflammatory response syndrome (SIRS) and multiple organ failure with potent insulinotropic activity, good bioavailability and low toxicity. Other specifically claimed compounds from this series of polyol succinates are:



Compound	R1=R2	R3	Formula
290200	H	H	C ₁₂ H ₁₆ O ₈
290201	Me	H	C ₁₄ H ₂₂ O ₈
290203	Me	Me	C ₁₅ H ₂₄ O ₈
290205	Me	CH ₂ OCOCH ₂ CH ₂ CO ₂ Et	C ₂₁ H ₃₂ O ₁₂
290208	H	Me	C ₁₃ H ₂₀ O ₈



Compound	R1	R2	R3	R4	Formula
290206	Me	Me	Me	Me	C ₂₄ H ₃₄ O ₁₆
290207	Et	Et	Et	Et	C ₂₈ H ₄₂ O ₁₆

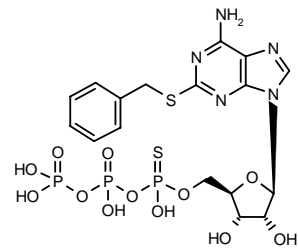
SOURCE – Leo.

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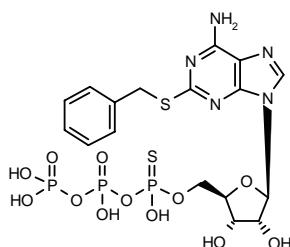
291492

2-Benzylsulfanyl-5'-O-(1-thiotriphosphate)adenosine isomer B



C17 H22 N5 O12 P3 S2; Mol wt: 645.4378

ACTION – Insulin segretagogue, a P2Y₁ receptor agonist able to induce a large biphasic and concentration-dependent (0.015-1.5 μ M) increase in glucose-induced insulin release in rat isolated pancreas, but also to increase pancreatic vascular resistance. Potentially useful for the treatment of type 2 diabetes, although the vascular effects may limit its use. The other isomer and the racemic compound show a similar profile.



291493: C17 H22 N5 O12 P3 S2: isomer A

SOURCES – Bar-Ilan University, Ramat-Gan (IL); Université Montpellier I, Montpellier (FR).

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INSULIN GLARGINE

Prop INN

215931

[Gly(A21),Arg(B31,B32)]-insulin (human)

21A-Glycine-30Ba-L-arginine-30Bb-L-arginineinsulin (human)

Hoe-71GT⁺

Hoe-901

ACTION – Recombinant human insulin analogue.

INDICATION – Once-daily s.c. administration at bedtime in the treatment of adults and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal insulin for the control of hyperglycemia.

PRESENTATION – Vials (5 and 10 ml) and cartridges (3 ml) containing sterile solution for injection, 100 IU/ml.

PROPRIETARY NAME – Lantus (DE).

SOURCE – Aventis Pharma.

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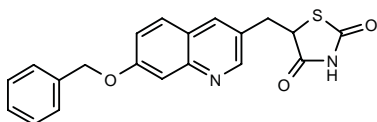
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*Drug Data Rep 1995, 017(03): 0268.

NC-2100*

237601

5-(7-Benzoyloxyquinolin-3-ylmethyl)thiazolidine-2,4-dione



C20 H16 N2 O3 S; Mol wt: 364.4234

ACTION – Antidiabetic agent, a thiazolidinedione derivative that weakly activates the peroxisome proliferator-activated receptor subtypes PPAR γ and PPAR α *in vitro*, as well as the transcription of PPAR γ target genes and adipocyte differentiation. In KKA γ obese mice, compound given in the diet for 1 or 2 weeks at a concentration of 0.1% significantly reduced glucose and triglyceride levels, with similar efficacy to pioglitazone 0.03% and greater efficacy than troglitazone 0.1%. Compound, like pioglitazone, decreased free fatty acid levels by nearly half and was associated with small increases in body weight and fat mass compared to troglitazone and pioglitazone, but a greater increase in food intake, suggesting that it stimulates energy expenditure. Similar to other thiazolidinediones and clofibrate, it increased uncoupling protein-2 (UCP2) mRNA levels in subcutaneous white adipose tissue (WAT), and it induced a small increase in UCP1 mRNA expression in brown adipose tissue (BAT), similar to thiazolidinediones. Only compound, however, significantly increased BAT-specific UCP1 mRNA in mesenteric and subcutaneous WAT.

SOURCE – Nippon Chemiphar.

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*Identified compound **237601** Drug Data Rep 1996, 018(09): 0809.

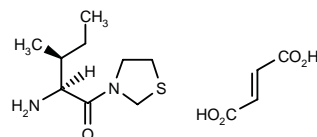
P32/98*

277261

2(S)-Amino-3(S)-methyl-1-(3-thiazolidinyl)pentan-1-one fumarate

3-(L-Isoleucyl)thiazolidine fumarate

3-[2(S)-Amino-3(S)-methylpentanoyl]thiazolidine fumarate



C9 H18 N2 O S . C4 H4 O4; Mol wt: 318.3918

ACTION – Antidiabetic agent, an inhibitor of dipeptidyl-peptidase IV (IC₅₀ = 2.8 μ M) proven to stabilize the gut insulinotropic peptide hormones GIP (glucose-dependent insulinotropic polypeptide) and glucagon-like peptide 1 (GLP-1). When given to diabetic Zucker rats (2.5 μ mol/300 g body weight p.o.) before an oral glucose tolerance test, it significantly improved glucose tolerance and enhanced insulin secretion. The glucose-lowering effect of the compound was demonstrated in both normal rats and obese Zucker rats. Compound is undergoing phase II clinical studies for the treatment of type 2 diabetes.

SOURCE – Probiobdrug.

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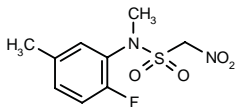
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- *Identified compound **277261** Drug Data Rep 1999, 021(07): 0619.

TREATMENT OF DIABETIC COMPLICATIONS

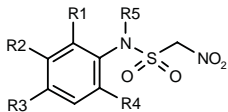
289929

N-(2-Fluoro-5-methylphenyl)-N-methylnitromethanesulfonamide



C9 H11 F N2 O4 S; Mol wt: 262.2599

ACTION – Agent for the treatment of diabetic complications, an aldose reductase inhibitor (IC₅₀ = 0.35 μM against enzyme from rat lens). Other compounds from this series of nitromethylsulfonamide derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
289930	H	H	H	H	H	C ₇ H ₈ N ₂ O ₄ S
289931	H	H	H	H	Me	C ₈ H ₁₀ N ₂ O ₄ S
289932	H	H	H	H	Et	C ₉ H ₁₂ N ₂ O ₄ S
289933	H	H	Cl	H	H	C ₇ H ₇ ClN ₂ O ₄ S
289934	H	H	Cl	H	Me	C ₈ H ₉ ClN ₂ O ₄ S
289935	H	H	OMe	OMe	H	C ₉ H ₁₂ N ₂ O ₆ S
289936	H	H	OMe	OMe	Me	C ₁₀ H ₁₄ N ₂ O ₆ S
289937	Me	H	H	Me	H	C ₉ H ₁₂ N ₂ O ₄ S
289938	H	Me	H	F	H	C ₈ H ₉ FN ₂ O ₄ S
289939	H	OMe	H	Me	H	C ₉ H ₁₂ N ₂ O ₅ S
289940	H	OMe	H	Me	Me	C ₁₀ H ₁₄ N ₂ O ₅ S

SOURCE – Senju.

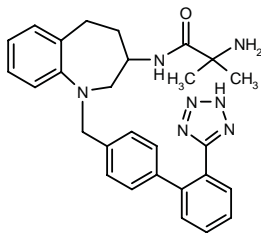
REFERENCES

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TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

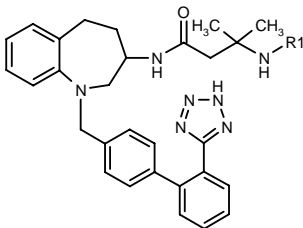
289622

2-Amino-2-methyl-N-[1-[2'-(2*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-3-yl]propionamide



C28 H31 N7 O; Mol wt: 481.6009

ACTION – Growth hormone (GH) secretagogue, potentially useful for increasing levels of endogenous GH, as well as for the treatment of obesity, osteoporosis, renal disease, cardiomyopathy, cachexia, HIV wasting syndrome, long-term critical illness, sarcopenia, syndrome X and diabetes, for stimulating wound healing and/or the immune system, and for increasing muscle mass and/or strength. Other specifically claimed compounds from this series of benzazepines and analogues are:



Compound	R1	Formula
289623	H	C ₂₉ H ₃₃ N ₇ O
289624	(R)-CH2CH(OH)Me	C ₃₂ H ₃₉ N ₇ O ₂

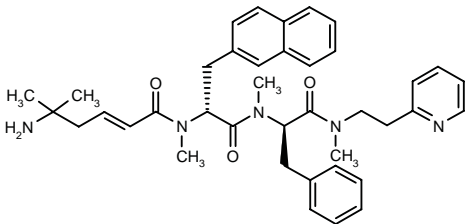
SOURCE – Bristol-Myers Squibb.

REFERENCES

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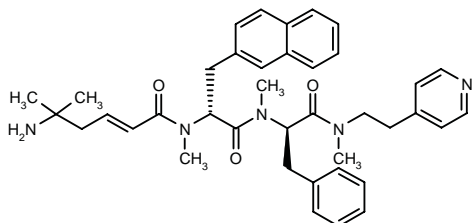
289795

N²-[N-[5-Amino-5-methyl-2(*E*)-hexenoyl]-N-methyl-3-(2-naphthyl)-D-alanyl]-N¹,N²-dimethyl-N¹-[2-(2-pyridyl)ethyl]-D-phenylalaninamide



C39 H47 N5 O3; Mol wt: 633.8323

ACTION – Growth hormone secretagogue useful for the treatment of growth hormone deficiency disorders and as a tool to study the regulation of growth hormone secretion at the pituitary level. The compound has good oral bioavailability and a relatively short plasma elimination half-life. Another specifically claimed compound is:



289796: C₃₉ H₄₇ N₅ O₃

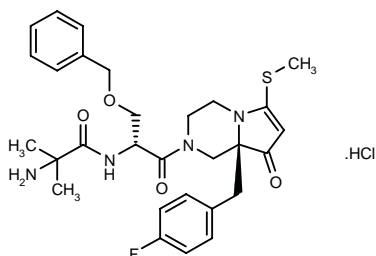
SOURCE – Novo Nordisk.

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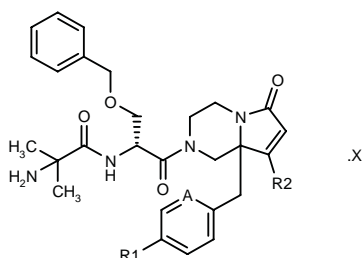
290037

2-Amino-*N*-[1(*R*)-(benzyloxymethyl)-2-[8a(*S*)-(4-fluoro-benzyl)-6-(methylsulfanyl)-8-oxo-1,2,3,4,8,8a-hexahydro-pyrrolo[1,2-*a*]pyrazin-2-yl]-2-oxoethyl]-2-methylpropionamide hydrochloride

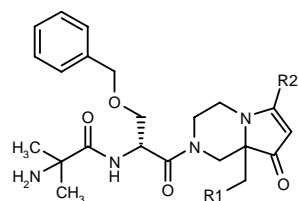


C₂₉ H₃₅ F N₄ O₄ S . HCl; Mol wt: 591.1444

ACTION – Growth hormone (GH) secretagogue with potential in the treatment of GH deficiencies, osteoporosis, congestive heart failure, obesity, frailty associated with aging, and AIDS- or cancer-associated cachexia, and for accelerating bone fracture repair, wound healing and the recovery of burn patients or patients after major surgery. Other exemplified compounds from this series of dipeptides include the following:



Compound	R1	R2	A	X	Formula
290038	H	OMe	N	HCl	C ₂₈ H ₃₅ N ₅ O ₅ ·HCl
290039	F	OMe	CH		C ₂₉ H ₃₅ FN ₄ O ₅
290040	H	H	CH		C ₂₈ H ₃₄ N ₄ O ₄



Compound	R1	R2	Formula
290041	4-F-Ph	N(Me) ₂	C ₃₀ H ₃₈ FN ₅ O ₄
290047	Ph	H	C ₂₈ H ₃₄ N ₄ O ₄
290048	2-Pyr	Me	C ₂₈ H ₃₅ N ₅ O ₄
290049	2-Pyr	t-Bu	C ₃₁ H ₄₁ N ₅ O ₄
290050	Ph	t-Bu	C ₃₂ H ₄₂ N ₄ O ₄
290051	H	Ph	C ₂₈ H ₃₄ N ₄ O ₄

SOURCE – Pfizer.

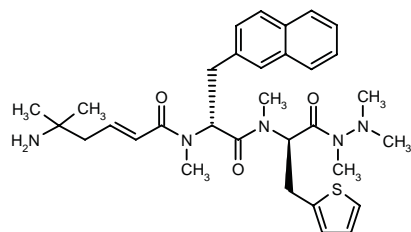
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NNC-26-1167

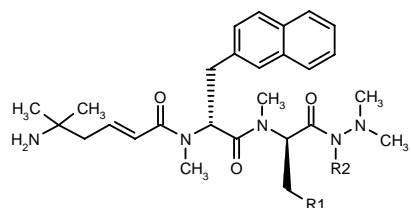
290168

1-[*N*-[5-Amino-5-methyl-2(*E*)-hexenoyl]-*N*-methyl-3-(2-naphthyl)-D-alanyl]-*N*-methyl-3-(2-thienyl)-D-alanyl]-1,2,2-trimethylhydrazine



C₃₂ H₄₃ N₅ O₃ S; Mol wt: 577.7897

ACTION – Growth hormone secretagogue with similar potency to the parent compound NN-703 (EC₅₀ = 9 and 8 nM, respectively, in rat pituitary cells; efficacy = 85 and 100%, respectively). In dogs, compound at 2-2.8 mg/kg p.o. showed improved potency with respect to GH release compared to NN-703. It exhibited the same oral bioavailability as NN-703, but a lower volume of distribution, associated with lower clearance and a shorter half-life. Other NN-703 derivatives are:



Compound	R1	R2	Formula
NNC-26-1089 [290164]	Ph	Me	C ₃₄ H ₄₅ N ₅ O ₃
NNC-26-1136 [290165]	Ph	H	C ₃₃ H ₄₃ N ₅ O ₃
NNC-26-1137 [290166]	2-thienyl	H	C ₃₁ H ₄₁ N ₅ O ₃ S

SOURCE – Novo Nordisk.

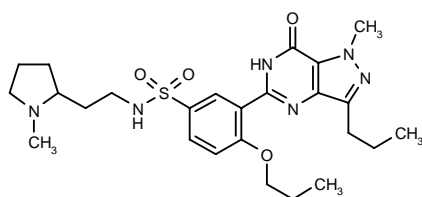
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TREATMENT OF MALE SEXUAL DYSFUNCTION

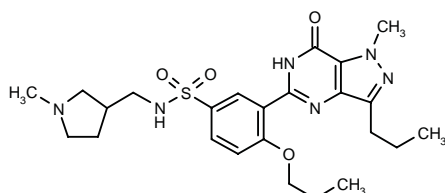
290189

3-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo-[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide



C25 H36 N6 O4 S; Mol wt: 516.6634

ACTION – Agent for the treatment of impotence, a selective inhibitor of phosphodiesterase type 5 (PDE5) with increased potency and selectivity over PDE3 and PDE6, as well as improved water solubility and decreased liver metabolism compared to sildenafil. *In vitro*, compound inhibited PDE5, PDE3 and PDE6 with IC₅₀ values of 4.57 ± 0.04 ng/ml, 36.2 ± 1.58 µg/ml and 126.9 ± 8.02 ng/ml, respectively, compared to respective values of 7.84 ± 0.32 ng/ml, 33.9 ± 1.64 µg/ml and 76.7 ± 1.53 ng/ml for sildenafil. *In vivo*, it was also found to be more potent than sildenafil in inducing penile erections in rats at 10 mg/kg p.o. LD₅₀ > 1 g/kg following oral administration in rats. In addition and contrary to sildenafil, it exhibited low liver metabolism when incubated in rat liver homogenates in the presence of NADPH. Another exemplified compound from this series of pyrazolopyrimidinone derivatives is:



290190: C24 H34 N6 O4 S

SOURCE – Dong-A.

REFERENCES

1. Yoo, M. et al. (Dong-A Pharmaceutical Co., Ltd.) *Pyrazolopyrimidinone derivs. for the treatment of impotence*. WO 0027848.

ANDROGEL™

272883

Testosterone gel

ACTION – Androgenic formulation that delivers physiological amounts of testosterone.

INDICATION – Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

PRESENTATION – Unit-dose packets of gel containing 1% testosterone, 2.5 g delivering 25 mg and 5.0 g delivering 50 mg.

PROPRIETARY NAME – AndroGel (US).

SOURCE – Unimed.

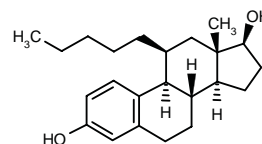
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8. *Unimed submits NDA for AndroGel*. DailyDrugNews.com (Daily Essentials) 1999, May 4.
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TREATMENT OF GYNECOLOGICAL DISORDERS

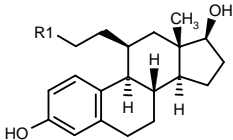
290476

11β-Pentylestra-1,3,5(10)-triene-3,17β-diol



C23 H34 O2; Mol wt: 342.5196

ACTION – Mixed estrogen receptor ER α agonist and ER β antagonist, potentially useful for the treatment of estrogen-related disorders such as menopausal complaints and osteoporosis, and in contraception, with reduced estrogen-related side effects. In addition, it is reported to be useful in the treatment or prevention of Alzheimer's disease, breast cancer, benign prostatic hypertrophy and cardiovascular disorders. Other exemplified compounds from this series of 11 β -substituted estradiol derivatives include the following:



Compound	R1	Formula
290477	allyl	C ₂₃ H ₃₂ O ₂
290478	1-propynyl	C ₂₃ H ₃₀ O ₂
290479	ethynyl-CH ₂	C ₂₃ H ₃₀ O ₂
290480	cyclopropylidene=CH	C ₂₄ H ₃₂ O ₂

SOURCE – Akzo Nobel.

REFERENCES

1. Loozen, H.J.J. and Schoonen, W.G.E.J. (Akzo Nobel N.V.) *Estrogenic estra-1,3,5(10)-trienes with differential effects on the alpha and beta estrogen receptors, having a linear hydrocarbon chain of from 5-9 carbon atoms in position 11.* WO 0031112.

AGENTS FOR FEMALE INFERTILITY

GANIRELIX ACETATE⁺

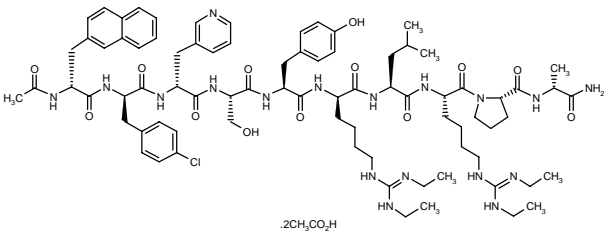
Rec INN; BANM; USAN

180634

N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N⁶-[(ethylamino)-(ethylimino)methyl]-D-lysyl-L-leucyl-N⁶-[(ethylamino)-(ethylimino)methyl]-L-lysyl-L-prolyl-D-alaninamide diacetate

N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-N^ω,N^ω-diethyl-D-homoarginyl-L-leucyl-N^ω,N^ω-diethyl-L-homoarginyl-L-prolyl-D-alaninamide diacetate

Org-37462
RS-26306
AntagonTM



C80 H113 Cl N18 O13 . 2 C2 H4 O2; Mol wt: 1690.4420

ACTION – Luteinizing hormone-releasing hormone (LHRH) antagonist, a synthetic decapeptide that induces rapid and reversible suppression of gonadotropin secretion.

INDICATION – Inhibition of premature LH surges in women undergoing controlled ovarian hyperstimulation.

PRESENTATION – Prefilled syringes (1 ml) for s.c. administration, 250 µg/0.5 ml.

PROPRIETARY NAME – Orgalutran (DE).

SOURCE – Organon.

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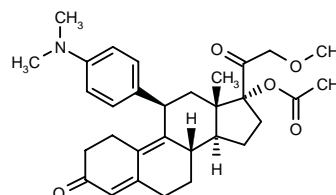
*Drug Data Rep 1992, 014(07): 0604.

CONTRACEPTIVES

CDB-4124

290664

17 α -Acetoxy-11 β -[4-(dimethylamino)phenyl]-21-methoxy-19-norpregna-4,9-diene-3,20-dione



C31 H39 N O5; Mol wt: 505.6511

ACTION – Contraceptive and antifertility agent, an analogue of CDB-2914 with superior antiprogesterinic activity in the rabbit Clauberg assay after both oral and intrauterine administration. In rats, compound given orally at a dose of 1 mg on the day of proestrus completely blocked ovulation, whereas CDB-2914 required a higher dose of 2 mg and mifepristone was not effective. However, in a postcoital antifertility assay, compound was less potent than CDB-2914: it prevented pregnancy in 10 of 10 mated rats at a dose of 4 mg/day p.o. on days 0-3 after mating, and in 7 of 10 animals treated at the lower dose of 2 mg/day, whereas CDB-2914 was completely effective at the dose of 2 mg/day. Compared to CDB-2914, compound was associated with less antiglucocorticoid activity and no glucocorticoid, estrogenic or androgenic activity; slight antiandrogenic and antiestrogenic effects were observed.

SOURCES – Department of Health & Human Services (US); National Institute of Child Health, Rockville, MD (US).

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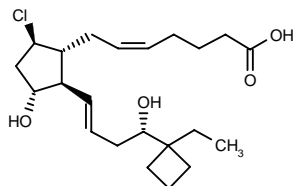
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UTERINE STIMULANTS AND TOCOLYTICS

ONO-8815^{1,3,4}

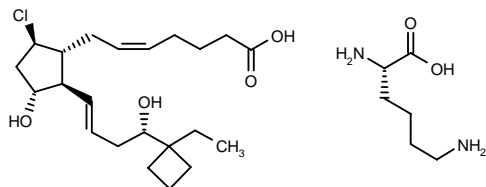
294995

9-Chloro-9,15-dideoxy-16(S)-(1-ethylcyclobutyl)-16-hydroxy-17,18,19,20-tetranorprostaglandin F_{2β}



C₂₂ H₃₅ Cl O₄; Mol wt: 398.9675

ACTION – Selective prostaglandin EP₂ receptor agonist with high nanomolar affinity for both human and mouse EP₂ receptors and low affinity for other EP subtypes (EP₁, EP_{3α} and EP₄), as well as prostanoid receptors (FP, IP and TP) and mouse DP receptors. In *in vitro* functional studies in cells expressing EP₂ receptors, compound stimulated cAMP production and was about 10- and 1,000-fold more potent than the EP₂ agonists butaprost and AH-13205, respectively. In anesthetized pregnant rats, compound, like butaprost, suppressed spontaneous uterine motility (ED₅₀ = 42 µg/kg i.v.) and was about 20-fold more potent than the tocolytic β₂-adrenoceptor agonist ritodrine (ED₅₀ = 922 µg/kg i.v.); in this model, it suppressed oxytocin- or PGF_{2α}-induced uterine motility. Its effects on uterine motility appeared to be mediated at least in part by elevation of cAMP levels, leading to smooth muscle relaxation. The L-lysine salt is also described:



ONO-8815Ly [276255]^{1,2,4}: C₂₂ H₃₅ Cl O₄ . C₆ H₁₄ N₂ O₂

SOURCE – Ono.

REFERENCES

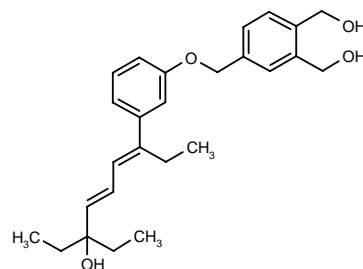
1. Tani, K. and Ohuchida, S. (Ono Pharmaceutical Co., Ltd.) *ω*-Cycloalkyl-prostaglandin E₂ derivs. EP 0860430, JP 1999193268, JP 2000128858, US 6110969..
2. Nitta, H. et al. *Inhibitory effect of ONO-8815Ly, a novel EP2 receptor agonist, on the motility of isolated pregnant rat uterus.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-604.
3. Ogawa, M. et al. *Development of ONO-8815, a potent and selective agonist of the prostaglandin E receptor EP₂ subtype.* 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 51.
4. Tani, K. et al. *Synthesis and structure activity relationships of potent and selective EP2 receptor agonists.* 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 51.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

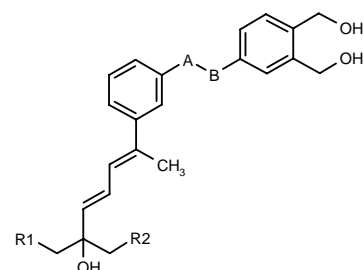
289853

(4*E*,6*E*)-7-[3-[3,4-Bis(hydroxymethyl)benzyloxy]phenyl]-3-ethyl-4,6-nonadien-3-ol

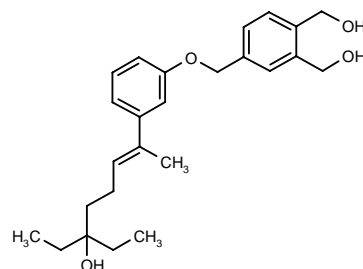


C₂₆ H₃₄ O₄; Mol wt: 410.5506

ACTION – Vitamin D analogue with potential in the treatment of dermal conditions such as acne and psoriasis, cancer, inflammatory and autoimmune diseases, endocrine disorders and bone disorders. *In vivo*, compound exhibited comparable potency to calcitriol in inducing 24-hydroxylase mRNA expression in the epidermis of mice following topical application at 0.1% w/v. Other exemplified compounds from this series of vitamin D analogues include the following:



Compound	R1=R2	A	B	Formula
289854	H	O	CH ₂	C ₂₃ H ₂₈ O ₄
289855	Me	CH ₂	CH ₂	C ₂₆ H ₃₄ O ₃
289857	Me	CH ₂	O	C ₂₅ H ₃₂ O ₄



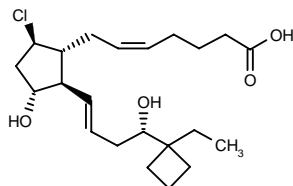
289856: C₂₅ H₃₄ O₄

UTERINE STIMULANTS AND TOCOLYTICS

ONO-8815^{1,3,4}

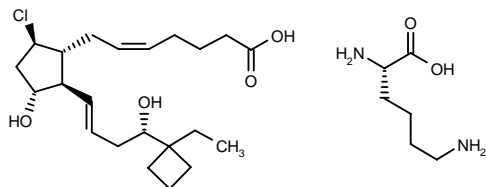
294995

9-Chloro-9,15-dideoxy-16(S)-(1-ethylcyclobutyl)-16-hydroxy-17,18,19,20-tetranorprostaglandin F_{2β}



C22 H35 Cl O4; Mol wt: 398.9675

ACTION – Selective prostaglandin EP₂ receptor agonist with high nanomolar affinity for both human and mouse EP₂ receptors and low affinity for other EP subtypes (EP₁, EP_{3α} and EP₄), as well as prostanoid receptors (FP, IP and TP) and mouse DP receptors. In *in vitro* functional studies in cells expressing EP₂ receptors, compound stimulated cAMP production and was about 10- and 1,000-fold more potent than the EP₂ agonists butaprost and AH-13205, respectively. In anesthetized pregnant rats, compound, like butaprost, suppressed spontaneous uterine motility (ED₅₀ = 42 µg/kg i.v.) and was about 20-fold more potent than the tocolytic β₂-adrenoceptor agonist ritodrine (ED₅₀ = 922 µg/kg i.v.); in this model, it suppressed oxytocin- or PGF_{2α}-induced uterine motility. Its effects on uterine motility appeared to be mediated at least in part by elevation of cAMP levels, leading to smooth muscle relaxation. The L-lysine salt is also described:



ONO-8815Ly [276255]^{1,2,4}: C22 H35 Cl O4 . C6 H14 N2 O2

SOURCE – Ono.

REFERENCES

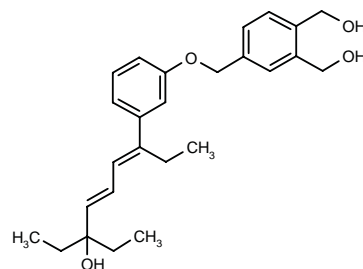
1. Tani, K. and Ohuchida, S. (Ono Pharmaceutical Co., Ltd.) *ω*-Cycloalkyl-prostaglandin E₂ derivs. EP 0860430, JP 1999193268, JP 2000128858, US 6110969..
2. Nitta, H. et al. *Inhibitory effect of ONO-8815Ly, a novel EP2 receptor agonist, on the motility of isolated pregnant rat uterus.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-604.
3. Ogawa, M. et al. *Development of ONO-8815, a potent and selective agonist of the prostaglandin E receptor EP₂ subtype.* 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 51.
4. Tani, K. et al. *Synthesis and structure activity relationships of potent and selective EP2 receptor agonists.* 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 51.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

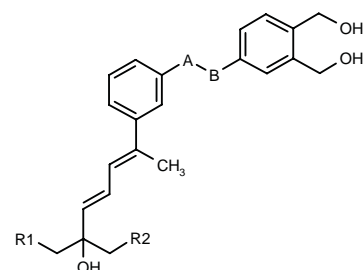
289853

(4*E*,6*E*)-7-[3-[3,4-Bis(hydroxymethyl)benzyloxy]phenyl]-3-ethyl-4,6-nonadien-3-ol

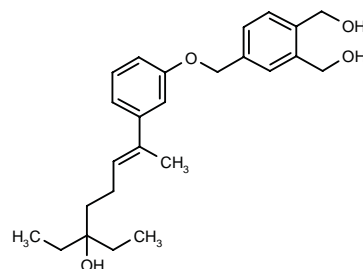


C26 H34 O4; Mol wt: 410.5506

ACTION – Vitamin D analogue with potential in the treatment of dermal conditions such as acne and psoriasis, cancer, inflammatory and autoimmune diseases, endocrine disorders and bone disorders. *In vivo*, compound exhibited comparable potency to calcitriol in inducing 24-hydroxylase mRNA expression in the epidermis of mice following topical application at 0.1% w/v. Other exemplified compounds from this series of vitamin D analogues include the following:



Compound	R1=R2	A	B	Formula
289854	H	O	CH2	C ₂₃ H ₂₈ O ₄
289855	Me	CH2	CH2	C ₂₆ H ₃₄ O ₃
289857	Me	CH2	O	C ₂₅ H ₃₂ O ₄



289856: C25 H34 O4

SOURCE – Galderma.

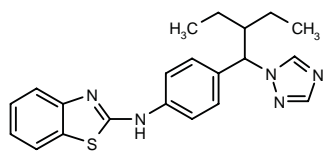
REFERENCES

1. Bernardon, J.-M. (CIRD Galderma) *Vitamin D analogues*. FR 2785284, WO 0026167.

R-115866*

262560

N-(2-Benzothiazolyl)-N-[4-[2-ethyl-1-(1,2,4-triazol-1-yl)butyl]phenyl]amine isomer B



C21 H23 N5 S; Mol wt: 377.5137

ACTION – Compound with retinoid-like effects and the ability to inhibit cytochrome P-450-mediated metabolism of retinoic acid ($IC_{50} = 4\text{ nM}$ for inhibition of cytochrome CYP26 isoenzyme). When given orally to rats, it induced a marked and transient increase in endogenous retinoic acid levels in plasma, skin, fat, kidney and testis. In addition, compound was found to exert retinoid-like activities such as inhibition of vaginal keratinization in estrogen-stimulated rats ($ED_{50} = 1\text{ mg/kg p.o.}$), induction of epidermal hyperplasia in mouse ear skin, upregulation of CYP26 mRNA expression in rat liver and transformation of mouse tail epidermis from a para- to an orthokeratotic skin type; these activities could be reversed by concomitant administration of the retinoic acid receptor (RAR) antagonist AGN-193109, indicating that the pharmacological activities of compound result from increased availability of retinoic acid and improved RAR triggering. Potentially useful for the treatment of cutaneous disorders including psoriasis and ichthyosis.

SOURCE – Janssen.

REFERENCES

1. Venet, M.G. et al. (Janssen Pharmaceutica NV) *N-[4-(Heteroaryl(methyl)phenyl)]-heteroarylamines*. EP 0907650, JP 2000503670, WO 9749704.

2. Stoppie, P. et al. *R115866 inhibits all-trans-retinoic acid metabolism and exerts retinoidal effects in rodents*. J Pharmacol Exp Ther 2000, 293(1): 304.

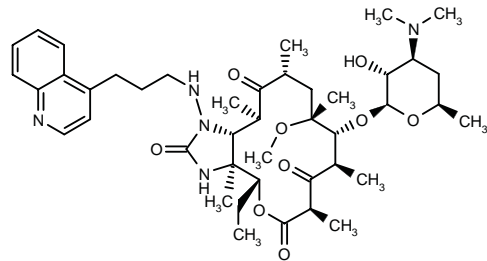
*Identified compound **262560** (see **260194**) Drug Data Rep 1998, 020(05): 0421.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

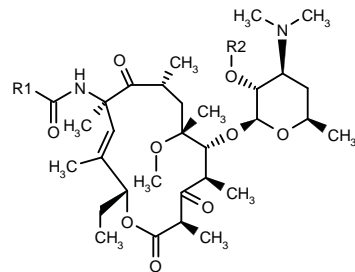
289722

12-Amino-11,12-dideoxy-3-des(hexopyranosyloxy)-6-O-methyl-3-oxo-11-[N²-[3-(8-quinoliny)propyl]hydrazino]-erythromycin A 11-N¹,12-N-carbodi- amide

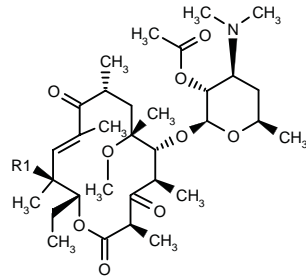


C43 H65 N5 O9; Mol wt: 796.0125

ACTION – Ketolide antibiotic for the treatment of bacterial and protozoal infections, also claimed for the therapy of cancer, particularly non-small cell lung cancer. Other macrolide antibiotics include the following:



Compound	R1	R2	Formula
289723	4-(3-Pyr)-1-imidazolyl-(CH2)4NH	H	C ₄₃ H ₆₆ N ₆ O ₉
289726	Me	Ac	C ₃₄ H ₅₆ N ₂ O ₁₀



Compound	R1	Formula
289724	N3	C ₃₂ H ₅₂ N ₄ O ₉
289725	NHAc	C ₃₄ H ₅₆ N ₂ O ₁₀
289727	-NCS	C ₃₃ H ₅₂ N ₂ O ₉ S

SOURCE – Galderma.

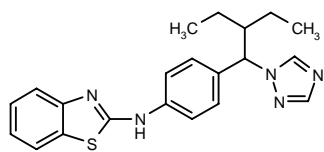
REFERENCES

1. Bernardon, J.-M. (CIRD Galderma) *Vitamin D analogues*. FR 2785284, WO 0026167.

R-115866*

262560

N-(2-Benzothiazolyl)-N-[4-[2-ethyl-1-(1,2,4-triazol-1-yl)butyl]phenyl]amine isomer B



C21 H23 N5 S; Mol wt: 377.5137

ACTION – Compound with retinoid-like effects and the ability to inhibit cytochrome P-450-mediated metabolism of retinoic acid ($IC_{50} = 4\text{ nM}$ for inhibition of cytochrome CYP26 isoenzyme). When given orally to rats, it induced a marked and transient increase in endogenous retinoic acid levels in plasma, skin, fat, kidney and testis. In addition, compound was found to exert retinoid-like activities such as inhibition of vaginal keratinization in estrogen-stimulated rats ($ED_{50} = 1\text{ mg/kg p.o.}$), induction of epidermal hyperplasia in mouse ear skin, upregulation of CYP26 mRNA expression in rat liver and transformation of mouse tail epidermis from a para- to an orthokeratotic skin type; these activities could be reversed by concomitant administration of the retinoic acid receptor (RAR) antagonist AGN-193109, indicating that the pharmacological activities of compound result from increased availability of retinoic acid and improved RAR triggering. Potentially useful for the treatment of cutaneous disorders including psoriasis and ichthyosis.

SOURCE – Janssen.

REFERENCES

1. Venet, M.G. et al. (Janssen Pharmaceutica NV) *N-[4-(Heteroaryl(methyl)phenyl)]-heteroarylamines*. EP 0907650, JP 2000503670, WO 9749704.

2. Stoppie, P. et al. *R115866 inhibits all-trans-retinoic acid metabolism and exerts retinoidal effects in rodents*. J Pharmacol Exp Ther 2000, 293(1): 304.

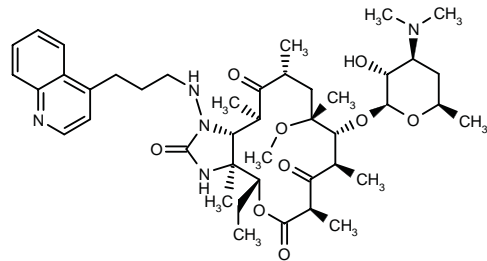
*Identified compound **262560** (see **260194**) Drug Data Rep 1998, 020(05): 0421.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

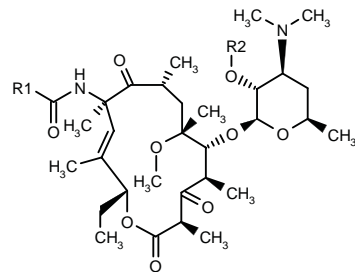
289722

12-Amino-11,12-dideoxy-3-des(hexopyranosyloxy)-6-O-methyl-3-oxo-11-[N²-[3-(8-quinoliny)propyl]hydrazino]-erythromycin A 11-N¹,12-N-carbodiimide

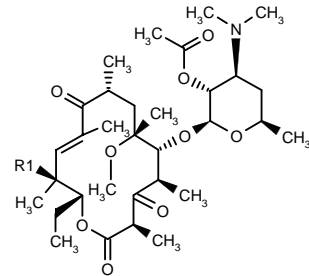


C43 H65 N5 O9; Mol wt: 796.0125

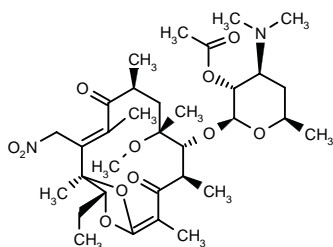
ACTION – Ketolide antibiotic for the treatment of bacterial and protozoal infections, also claimed for the therapy of cancer, particularly non-small cell lung cancer. Other macrolide antibiotics include the following:



Compound	R1	R2	Formula
289723	4-(3-Pyr)-1-imidazolyl-(CH2)4NH	H	C ₄₃ H ₆₆ N ₆ O ₉
289726	Me	Ac	C ₃₄ H ₅₆ N ₂ O ₁₀



Compound	R1	Formula
289724	N3	C ₃₂ H ₅₂ N ₄ O ₉
289725	NHAc	C ₃₄ H ₅₆ N ₂ O ₁₀
289727	-NCS	C ₃₃ H ₅₂ N ₂ O ₉ S



289729: C33 H52 N2 O11

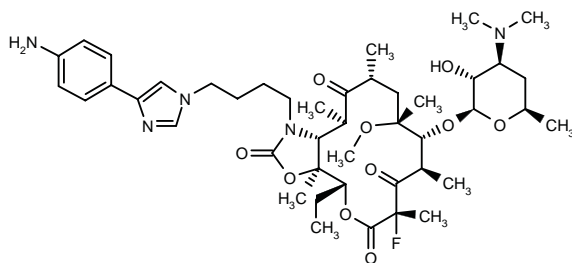
SOURCE – Pfizer.

REFERENCES

1. Kaneko, T. (Pfizer Products Inc.) *Novel macrolide antibiotics*. WO 0026224.

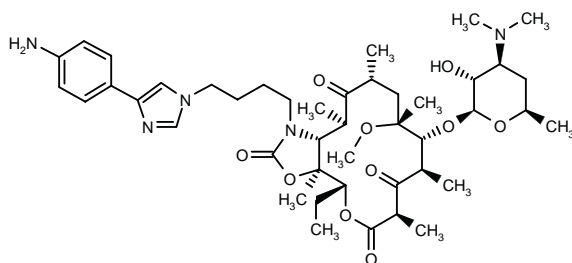
289954

11-[4-[4-(4-Aminophenyl)imidazol-1-yl]butylamino]-11-deoxy-3-des(hexopyranosyloxy)-2-fluoro-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate



C44 H66 F N5 O10; Mol wt: 844.0284

ACTION – Macrolide antibiotic active against *Streptococcus pyogenes* and *Streptococcus pneumoniae* (MIC = 0.3 and 0.150 µg/ml, respectively). Another specifically claimed erythromycin derivative is:



289955: C44 H67 N5 O10

SOURCE – Aventis Pharma.

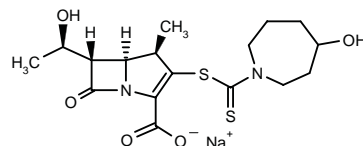
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1. Agouridas, C. et al. (Aventis Pharma SA) *Novel erythromycin derivs., preparation method and use as medicines*. EP 1016669, FR 2785612, JP 2000143689, WO 0027857.

290126

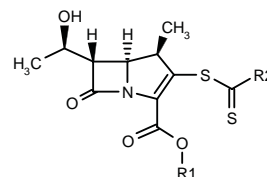
(4*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-3-(4-hydroxy-perhydroazepin-1-ylcarbothioylsulfanyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid sodium salt

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-(4-hydroxyperhydroazepin-1-ylcarbothioylsulfanyl)-1-methyl-1-carba-2-penem-3-carboxylic acid sodium salt

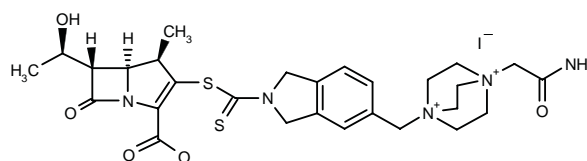


C17 H23 N2 Na O5 S2; Mol wt: 422.4997

ACTION – Carbapenem antibiotic and metallo-β-lactamase inhibitor that exhibits potent *in vitro* activity against *Staphylococcus aureus* MB4970, *S. aureus* JS1, *S. aureus* BB5939 and *Proteus mirabilis* MB4955 (MIC = 0.025, 0.1, 1.56 and 0.05 µg/ml, respectively); it was devoid of CNS toxicity in rats and did not exhibit any signs of toxicity in mice at doses up to 2000 mg/kg i.v. Other exemplified compounds include the following:



Compound	R1	R2	Formula
290127	H	N(Me)CH2CH2OH	C ₁₄ H ₂₀ N ₂ O ₅ S ₂
290128	H	4-(MeNHCH2CO)-1-Piz	C ₁₈ H ₂₈ N ₄ O ₅ S ₂
290130	Na	N(Me) ₂	C ₁₃ H ₁₇ N ₂ NaO ₄ S ₂
290153	H	4-(NH2CH2)-1,2,3,6-tetrahydro-1-Pyr	C ₁₇ H ₂₃ N ₃ O ₄ S ₂



290152: C28 H36 I N5 O5 S2

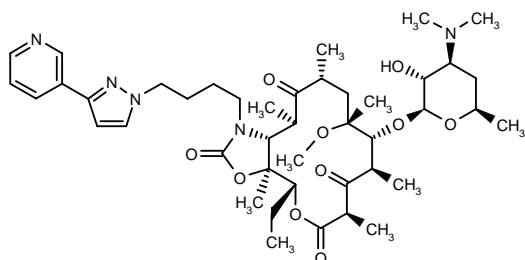
SOURCE – Banyu.

REFERENCES

1. Hashizume, T. and Nagano, R. (Banyu Pharmaceutical Co., Ltd.) *Metallo-β-lactamase inhibitors*. JP 2000136133.

290192

11-Deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxo-11-[4-[3-(3-pyridyl)pyrazol-1-yl]butylamino]erythro-mycin A 11-*N*,12-*O*-cyclic carbamate



C43 H65 N5 O10; Mol wt: 812.0115

ACTION – Erythromycin antibiotic active against several Gram-positive bacteria including strains of *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pneumoniae*, giving MIC values of 0.02-0.6 µg/ml, as well as against the Gram-negative microorganism *Haemophilus influenzae*.

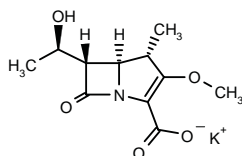
SOURCE – Aventis Pharma.

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1. Denis, A. (Aventis Pharma SA) *Derivs. of erythromycin, their process of preparation and their application as medicaments*. EP 1004592, FR 2786188, JP 2000159790.

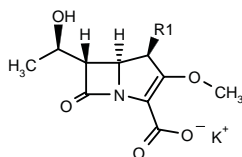
291256

(1*S*,5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-methoxy-1-methyl-1-carba-2-penem-3-carboxylic acid potassium salt



C11 H14 K N O5; Mol wt: 279.3316

ACTION – Carbapenem antibiotic with good antibacterial activity against Gram-positive bacteria including *Staphylococcus aureus* (MIC < 0.5 µg/ml), *Escherichia coli* TEM (MIC = 5 µg/ml) and *Staphylococcus* 25768 (MIC = 5 µg/ml). Compound was seen to strongly inhibit both class A β-lactamase of *E. coli* TEM (IC₅₀ = 0.23 µM) and class C β-lactamase of *Enterobacter cloacae* (IC₅₀ = 0.082 µM). Other related carbapenems are:



Compound	R1	Formula
291255	Me	C ₁₁ H ₁₄ KNO ₅
291257	H	C ₁₀ H ₁₂ KNO ₅

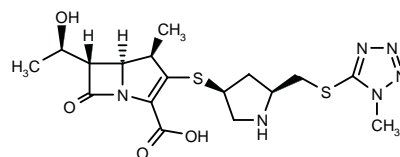
SOURCE – Ludwig-Maximilians-Universität München, Munich (DE).

REFERENCES

1. Pfändler, H.R. et al. *Synthesis and biological activities of an α-methyl and a β-methyl carbapenem and the corresponding unsubstituted compound*. Bioorg Med Chem Lett 2000, 10(12): 1389.

291267

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[5(*S*)-(1-methyl-1*H*-tetrazol-5-yl)sulfanylmethyl]pyrrolidin-3(*S*)-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid



C17 H24 N6 O4 S2; Mol wt: 440.5466

ACTION – Carbapenem antibiotic with broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria including *Streptococcus pyogenes* (MIC = 0.004 µg/ml), *Staphylococcus aureus* (MIC = 0.025-0.049 µg/ml), *Klebsiella aerogenes* (MIC = 0.025 µg/ml), *Escherichia coli* (MIC = 0.025 µg/ml) and *Pseudomonas aeruginosa* (MIC = 0.195-0.781 µg/ml). When compared with meropenem, compound showed 2-4-fold superior antibacterial activity, especially against Gram-positive bacteria. A good pharmacokinetic profile was observed after i.v. administration to rats, with a half-life and AUC approximately 3-fold higher than those of meropenem or imipenem.

SOURCE – Korea Institute of Science and Technology, Seoul (KR).

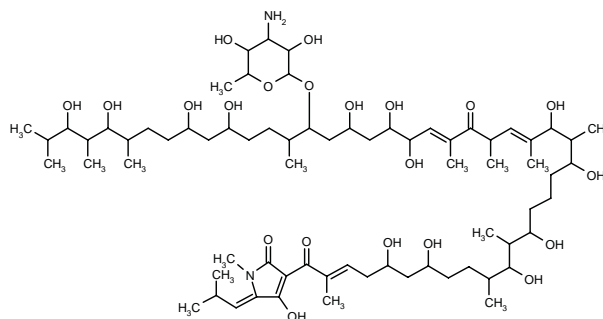
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1. Shin, K.J. et al. *Synthesis and biological properties of new 1β-methylcarbapenems having tetrazolothioether moiety*. Bioorg Med Chem Lett 2000, 10(13): 1421.

VANCORESMYCIN

289942

31-(4-Amino-3,5-dihydroxy-6-methyltetrahydro-2*H*-pyran-2-yloxy)-5,7,11,13,17,19,26,27,29,35,37,41,43-tridecahydroxy-1-[3-hydroxy-1-methyl-2-[(*Z*)-2-methylpropylidene]-5-oxo-1,5-dihydro-2*H*-pyrrol-4-yl]-2,10,12,18,20,22,24,32,40,42,44-undecamethyl-2(*E*),20(*E*),24(*E*)-pentatetracontatriene-1,23-dione



C71 H126 N2 O21; Mol wt: 1343.7690

ACTION – Antibiotic obtained by culturing the micro-organism HIL-006734 (DSM-12216), found to be active against several strains of *Staphylococcus aureus* (MIC = 0.025-0.39 µg/ml), *Staphylococcus epidermidis* (MIC = 0.10-0.20 µg/ml) and *Enterococcus faecalis* (MIC = 0.39 µg/ml).

SOURCE – Aventis Pharma.

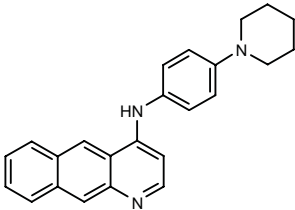
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1. Ramakrishna, N.V.S. et al. (Aventis Pharma Deutschland GmbH) *Vancoresmycin, a process for its production and its use as a pharmaceutical*. WO 0028064.

ANTIBACTERIAL DRUGS

289492

N-[4-(1-Piperidinyl)phenyl]benzo[g]quinolin-4-amine



C24 H23 N3; Mol wt: 353.4667

ACTION – Antibacterial agent that acts by selectively inhibiting bacterial RNA polymerases relative to human RNA polymerase, a representative compound from a series of benzoquinoline derivatives. *In vitro*, it exhibited potent antimicrobial activity against *Staphylococcus aureus* (MIC = 2 µg/ml, MBC = 4 µg/ml) and rifampicin-resistant *S. aureus* (MIC = 2 µg/ml, MBC = 2 µg/ml), being less effective against *Escherichia coli*.

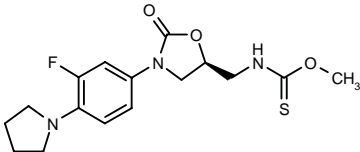
SOURCE – Scriptgen.

REFERENCES

1. Lam, K. et al. (Scriptgen Pharmaceuticals, Inc.) *Benzoquinoline derivs. useful as antibacterial agents*. WO 0024389.

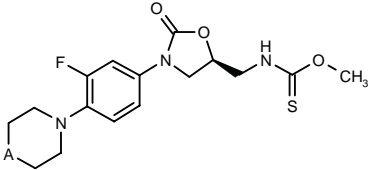
289918

N-[3-[3-Fluoro-4-(1-pyrrolidinyl)phenyl]-2-oxooxazolidin-5(S)-ylmethyl]thiocarbamic acid O-methyl ester



C16 H20 F N3 O3 S; Mol wt: 353.4160

ACTION – Antimicrobial agent proven active against several strains of *Staphylococcus aureus*, *Bacillus subtilis*, methicillin-resistant *S. aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis* and *Enterococcus faecium*, with MIC values of 0.39 µg/ml. It also gave MIC values of 0.78-1.56 µg/ml against atypical acid-fast bacteria strains of *Mycobacterium avium* and *Mycobacterium intracellulare*. Other exemplified thiocarbamic acid derivatives include the following:



Compound	A	Formula
289919	S	C ₁₆ H ₂₀ FN ₃ O ₃ S ₂
289920	SO	C ₁₆ H ₂₀ FN ₃ O ₄ S ₂
289921	SO2	C ₁₆ H ₂₀ FN ₃ O ₅ S ₂

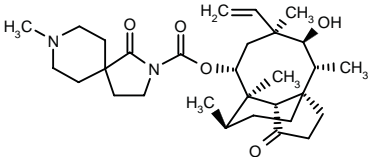
SOURCE – Hokuriku.

REFERENCES

1. Kado, N. et al. (Hokuriku Seiyaku Co., Ltd.) *Thiocarbamic acid derivs.* JP 2000204084, WO 0027830.

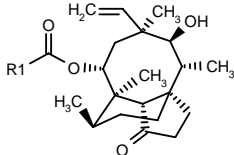
289974

8-Methyl-1-oxo-2,8-diazaspiro[4.5]decane-2-carboxylic acid (1*S*,2*R*,3*S*,4*S*,6*R*,7*R*,8*S*,14*R*)-3-hydroxy-2,4,7,14-tetramethyl-9-oxo-4-vinyltricyclo[5.4.3.0^{1,8}]tetradec-6-yl ester



C30 H46 N2 O5; Mol wt: 514.7024

ACTION – Antimicrobial agent specifically claimed for the therapy of recurrent sinusitis and otitis media, skin and soft tissue infections and acne. Other compounds from this series of mutilin derivatives are:



Compound	R1	Formula
289975	8-Me-1,3-dioxo-2,8-diazaspiro[4.5]dec-2-yl	C ₃₀ H ₄₄ N ₂ O ₆
289976	8-(t-BuOCOCH2)-1-oxo-2,8-diazaspiro[4.5]dec-2-yl	C ₃₅ H ₅₄ N ₂ O ₇
289977	4-(1-Me-4-Pip-CH2O)-PhCH2	C ₃₅ H ₅₁ NO ₅
289978	2-(4-Pip)-4-thiazolyl-CH2	C ₃₀ H ₄₄ N ₂ O ₄ S
289979	4-[N(Me)2CH2CH2]-PhOCH2	C ₃₂ H ₄₇ NO ₅
289981	4-[N(Me)2CH2CH2NHCO]-PhOCH2	C ₃₃ H ₄₈ N ₂ O ₆

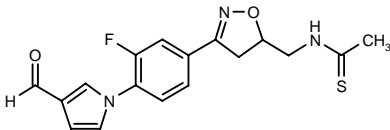
SOURCE – SmithKline Beecham.

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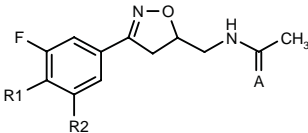
290018

(±)-N-[3-[3-Fluoro-4-(3-formyl-1*H*-pyrrol-1-yl)phenyl]-4,5-dihydro-5-isoxazolylmethyl]thioacetamide



C17 H16 F N3 O2 S; Mol wt: 345.3964

ACTION – Antibacterial agent active *in vitro* against *Staphylococcus aureus* UC-9213, *S. aureus* UC-12673, *Streptococcus pneumoniae* UC-9912 and *Enterococcus faecalis* UC-9217 (MIC < 0.125-0.25 µg/ml). Other exemplified substituted aminophenyl isoxazoline derivatives include the following:



Compound	R1	R2	A	Isomer	Formula
290019	3-CHO-1-pyrrolyl	H	O	(-)	C ₁₇ H ₁₆ FN ₃ O ₃
290020	3-(C=NOH)-1-pyrrolyl	H	O	(-)	C ₁₇ H ₁₇ FN ₄ O ₃
290021	3-CN-1-pyrrolyl	H	O	(-)	C ₁₇ H ₁₅ FN ₄ O ₂
290022	1-pyrrolyl	H	S	(-)	C ₁₆ H ₁₆ FN ₃ OS
290023	4-morpholinyl	F	S	(-)	C ₁₆ H ₁₉ F ₂ N ₃ O ₂ S

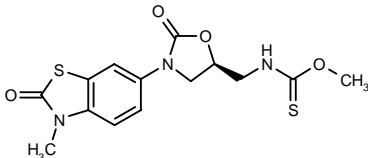
SOURCE – Pharmacia.

REFERENCES

1. Barbachyn, M.R. et al. (Pharmacia & Upjohn Co.) *Substd. aminophenyl isoxazoline derivs. useful as antimicrobials.* US 6069141.

290290

N-[3-(3-Methyl-2-oxo-2,3-dihydrobenzothiazol-6-yl)-2-oxooxazolidin-5(S)-ylmethyl]thiocarbamic acid *O*-methyl ester



C14 H15 N3 O4 S2; Mol wt: 353.4215

ACTION – A representative compound from a series of heterocyclyl-substituted oxazolidone antibacterials with an MIC value of 0.06 µg/ml against *Staphylococcus aureus* 133.

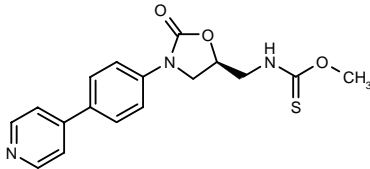
SOURCE – Bayer.

REFERENCES

1. Bartel, S. et al. (Bayer AG) *Novel heterocyclyl-substd. oxazolidone derivs.* WO 0029409.

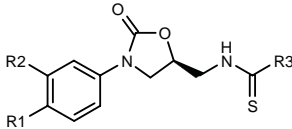
290291

N-[2-Oxo-3-[4-(4-pyridinyl)phenyl]oxazolidin-5(S)-ylmethyl]thiocarbamic acid *O*-methyl ester



C17 H17 N3 O3 S; Mol wt: 343.4053

ACTION – Antibacterial agent with an MIC value of 0.13 µg/ml against *Staphylococcus aureus* 133. Other specifically claimed substituted phenyloxazolidone derivatives include the following:



Compound	R1	R2	R3	Formula
290292	4-morpholinyl	F	OMe	C ₁₆ H ₂₀ FN ₃ O ₄ S
290293	3-oxo-1-cyclohexenyl	H	OMe	C ₁₈ H ₂₀ N ₂ O ₄ S
290294	Ac	H	OMe	C ₁₄ H ₁₆ N ₂ O ₄ S
290295	C(Me)=NOH	H	OMe	C ₁₄ H ₁₇ N ₃ O ₄ S
290296	(E)-C(Me)=CHCN	H	OMe	C ₁₆ H ₁₇ N ₃ O ₃ S
290297	(Z)-C(Me)=CHCN	H	OMe	C ₁₆ H ₁₇ N ₃ O ₃ S
290298	(E)-CH=C(Me)CN	H	OMe	C ₁₆ H ₁₇ N ₃ O ₃ S
290299	4-Pyr	H	NH2	C ₁₆ H ₁₆ N ₄ O ₂ S
290300	3-oxo-1-cyclohexenyl	H	NH2	C ₁₇ H ₁₉ N ₃ O ₃ S

SOURCE – Bayer.

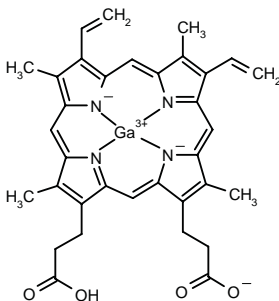
REFERENCES

1. Bartel, S. et al. (Bayer AG) *Novel substd. phenyloxazolidone derivs.* WO 0029396.

Ga-PPIX

289900

Hydrogen [3,8,13,17-Tetramethyl-7,12-vinyl-21*H*,23*H*-porphirin-2,18-dipropionato(4-)-κ*N*²¹,κ*N*²²,κ*N*²³,κ*N*²⁴]-gallate



C34 H31 Ga N4 O4; Mol wt: 629.3659

ACTION – Antibacterial protoporphyrin IX complex active against Gram-negative bacteria such as *Yersinia enterocolitica* H1852, methicillin-resistant Gram-positive strains such as *Staphylococcus aureus* IR219 and the acid-fast bacillus *Mycobacterium segmatis* LR222 (MIC = 0.4, 1.6 and 0.4 µg/ml, respectively).

SOURCE – Emory University, Atlanta, GA (US).

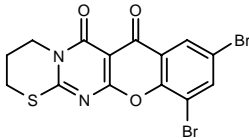
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ANTIMYCOBACTERIAL AGENTS

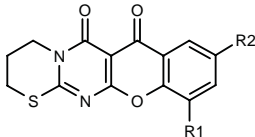
290246

9,11-Dibromo-3,4-dihydro-2*H*,6*H*,7*H*-1-benzopyran-[2',3':4,5]pyrimido[2,1-*b*][1,3]thiazine-6,7-dione



C14 H8 Br2 N2 O3 S; Mol wt: 444.1022

ACTION – Antimicrobial agent active against myco-bacteria including strains resistant to isoniazid, as well as viruses, particularly herpes simplex viruses, and *Chlamydia*; it also exhibits immunostimulating activity. Compound exhibited MIC values of 0.1 and 0.1 mg/l against *Mycobacterium tuberculosis* H37Rv and *Mycobacterium smegmatis* ATCC607, respectively, compared to respective MIC values of 0.1 and 1.5 mg/l for isoniazid, 0.2 and 0.15 mg/l for streptomycin and 0.05 and 0.25 mg/l for rifamycin. It also stimulated interferon production in human lymphocytes. In addition, it exhibited comparable activity to i.m. streptomycin in a murine model of experimental tuberculosis when given at 10-30 mg/kg p.o. No acute toxicity was observed in mice (LD₅₀ > 1500 mg/kg p.o. and i.p.). Other specifically claimed hetero-cyclic compounds include the following:



Compound	R1	R2	Formula
290247	H	H	C ₁₄ H ₁₀ N ₂ O ₃ S
290248	H	Cl	C ₁₄ H ₉ ClN ₂ O ₃ S
290249	Cl	Cl	C ₁₄ H ₈ Cl ₂ N ₂ O ₃ S
290250	H	Br	C ₁₄ H ₉ BrN ₂ O ₃ S
290251	H	NO ₂	C ₁₄ H ₉ N ₃ O ₅ S
290252	Cl	NO ₂	C ₁₄ H ₈ ClN ₃ O ₅ S
290253	Br	NO ₂	C ₁₄ H ₈ BrN ₃ O ₅ S
290254	H	OMe	C ₁₅ H ₁₂ N ₂ O ₄ S
290255	H	OH	C ₁₄ H ₁₀ N ₂ O ₄ S

SOURCE – Natural Drug Sciences.

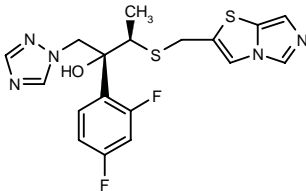
REFERENCES

1. Krasnov, K.A. and Ashkinazi, R.I. (Natural Drug Sciences LLC) *Biologically active substance on the basis of tetracyclic nitrogen heterocycles of pyrimidine row*. US 6071905, WO 9843982.

ANTIFUNGAL AGENTS

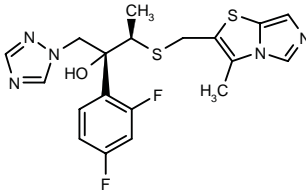
289997

2(*R*)-(2,4-Difluorophenyl)-3(*R*)-(imidazo[5,1-*b*]thiazol-2-ylmethylsulfanyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol



C18 H17 F2 N5 O S2; Mol wt: 421.4943

ACTION – Triazole antifungal agent with potent activity *in vitro* against *Candida albicans* TIMM1768 (IC₈₀ = 0.0039 µg/ml or less), *C. albicans* TIMM3163 (IC₈₀ = 0.5 µg/ml) and *Aspergillus fumigatus* TIMM1775 (IC₈₀ = 1 µg/ml) compared to IC₈₀ values of 0.5, > 128 and > 128 µg/ml, respectively, for fluconazole. *In vivo*, compound was active in murine models of systemic candidiasis and pulmonary aspergillosis, increasing life span by 306 and 60%, respectively, at 5 and 20 mg/kg p.o. Other exemplified compounds from this series of imidazo[5,1-*b*]thiazole derivatives include the following:



289998: C19 H19 F2 N5 O S2

SOURCE – Meiji Seika.

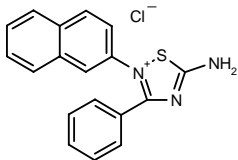
REFERENCES

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ANTIVIRAL DRUGS

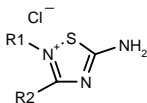
289588

5-Amino-2-(2-naphthyl)-3-phenyl-1,2,4-thiadiazol-2-ium chloride



C18 H14 Cl N3 S; Mol wt: 339.8486

ACTION – Antiviral agent for the treatment and prophylaxis of hepatitis C virus (HCV) infections with inhibitory activity against HCV NS3 helicase. *In vitro*, compound inhibited the ATPase and unwinding activities of the enzyme with IC₅₀ values < 25 μM. Other exemplified pentacyclic compounds include the following:



Compound	R1	R2	Formula
289589	3-Cl-Ph	Ph	C ₁₄ H ₁₁ Cl ₂ N ₃ S
289592	1-Naph	Ph	C ₁₈ H ₁₄ ClN ₃ S
289593	3-Me-Ph	Ph	C ₁₅ H ₁₄ ClN ₃ S
289594	3-Et-Ph	Ph	C ₁₆ H ₁₆ ClN ₃ S
289595	4-i-Pr-Ph	Ph	C ₁₇ H ₁₈ ClN ₃ S
289596	1-Naph-CH2	Ph	C ₁₉ H ₁₆ ClN ₃ S
289597	Ph	2-thienyl	C ₁₂ H ₁₀ ClN ₃ S ₂
289598	Ph	3-MeO-Ph	C ₁₅ H ₁₄ ClN ₃ OS
289599	2-fluorenyl	Ph	C ₂₁ H ₁₆ ClN ₃ S
289600	4-cyclohexyl-Ph	Ph	C ₂₀ H ₂₂ ClN ₃ S
289601	4-(PhCH2)-Ph	Ph	C ₂₁ H ₁₈ ClN ₃ S
289602	3-(CO2Me)-Ph	Ph	C ₁₆ H ₁₄ ClN ₃ O ₂ S

SOURCE – Vertex.

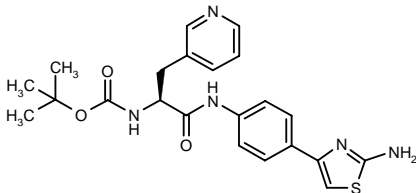
REFERENCES

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290234

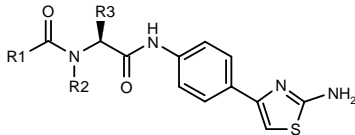
N-[2-[4-(2-Aminothiazol-4-yl)phenylamino]-2-oxo-1(*S*)-(3-pyridinylmethyl)ethyl]carbamic acid *tert*-butyl ester

*N*¹-[4-(2-Aminothiazol-4-yl)phenyl]-*N*²-(*tert*-butoxy-carbonyl)-3-(3-pyridyl)-L-alaninamide



C22 H25 N5 O3 S; Mol wt: 439.5375

ACTION – Antiviral agent for the treatment of herpesvirus infection that acts by inhibiting herpes helicase–primase enzyme complex. *In vitro*, compound inhibited herpes simplex virus type 1 (HSV-1) helicase–primase (IC₅₀ = 0.13 μM) and was shown to inhibit HSV-1 replication in cell culture (EC₅₀ = 0.043 μM), as well as human cytomegalovirus (CMV) replication using an ELISA-based assay (EC₅₀ = 20 μM). Other exemplified compounds from this series of non-nucleoside compounds include the following



Compound	R1	R2	R3	Formula
290235	4-quinolyl	CH2Ph	H	C ₂₈ H ₂₃ N ₅ O ₂ S
290236	t-BuO	H	3-indolyl-CH2	C ₂₅ H ₂₇ N ₅ O ₃ S

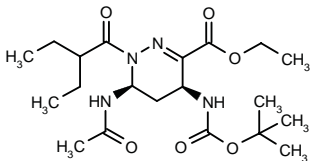
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Simoneau, B. et al. (Boehringer Ingelheim [Canada] Ltd.) *Antiherpes cpds*. WO 0029399.

290301

cis-6-Acetamido-4-(*tert*-butoxycarbonylamino)-1-(2-ethylbutyryl)-1,4,5,6-tetrahydropyridazine-3-carboxylic acid ethyl ester



C20 H34 N4 O6; Mol wt: 426.5106

ACTION – A representative compound from a series of 1,4,5,6-tetrahydropyridazine derivatives with neuraminidase-inhibitory activity, particularly active against influenza neuraminidase and thus expected to be of use for the treatment or prophylaxis of influenza infections.

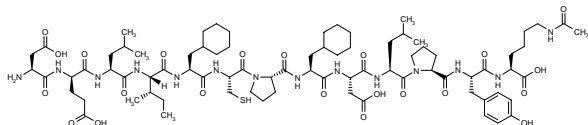
SOURCE – Gilead.

REFERENCES

1. Kim, C.U. and Lawton, G. (Gilead Sciences Inc.) *1,4,5,6-Tetrahydro-pyridazine derivs., their preparation and their use as neuraminidase inhibitors*. WO 0029385.

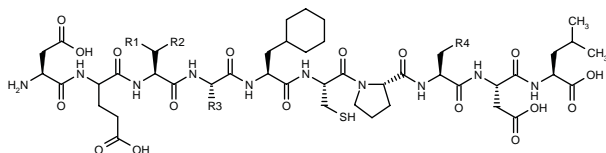
290489

L-Aspartyl-D-glutamyl-L-leucyl-L-isoleucyl-(3-cyclohexyl)-L-alanyl-L-cysteinyl-L-prolyl-(3-cyclohexyl)-L-alanyl-L-aspartyl-L-leucyl-L-prolyl-L-tyrosyl-*N*^ε-acetyl-L-lysine

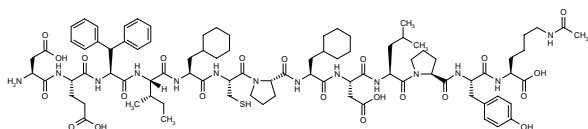


C79 H124 N14 O22 S; Mol wt: 1653.9910

ACTION – Agent for the treatment of hepatitis C or related conditions, a representative compound from a series of peptidic inhibitors of hepatitis C virus (HCV) NS3 protease which are based on the P and P' regions of the natural substrate. *In vitro*, it inhibited HCV NS3 protease with an IC₅₀ value of < 0.2 nM. Other exemplified peptides include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
290491	Ph	Ph	(S)-CH(Me)Et	cyclohexyl	L	C ₆₆ H ₉₆ N ₁₀ O ₁₇ S
290492	Ph	Ph	(S)-CH(Me)Et	Pr	L	C ₆₃ H ₉₂ N ₁₀ O ₁₇ S
290493	Ph	Ph	(S)-CH(Me)Et	CH2Ph	L	C ₆₇ H ₉₂ N ₁₀ O ₁₇ S
290495	i-Pr	H	(S)-CH(Me)Et	cyclohexyl	D	C ₅₇ H ₈₄ N ₁₀ O ₁₇ S
290496	i-Pr	H	CH2CH2CO2H	cyclohexyl	D	C ₅₆ H ₉₀ N ₁₀ O ₁₉ S



290494: C88 H126 N14 O22 S

SOURCE – Istituto di Ricerche di Biologia Molecolare P. Angeletti, Pomezia (IT).

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1. Pessi, A. et al. (Istituto di Ricerche di Biologia Molecolare P. Angeletti SpA) *Pharmaceutical cpds. for the inhibition of hepatitis C virus NS3 protease*. WO 0031129.

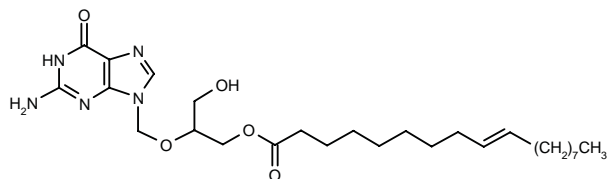
GANCICLOVIR ELAIDIC ACID

250436

Octadec-9(*E*)-enoic acid 2-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-ylmethoxy)-3-hydroxypropyl ester

E-GCV

P-4018



C27 H45 N5 O5; Mol wt: 519.6825

ACTION – Antiviral agent, the elaidic acid ester prodrug of ganciclovir proven to be 5-30-fold more effective than the parent compound against most strains of herpes simplex virus type 1 (HSV-1), with IC₅₀ values of 1, 0.2 and 0.5 nM, against KOS, Hu-3 and Hu-5 strains, respectively, in HEL cells. Compound was also significantly more active against certain HSV-2 strains including the G strain (IC₅₀ = 1.2 nM) and the thymidine kinase-positive (TK+) HS-47 strain (IC₅₀ = 0.6 nM) in HEL cells, whereas it had similar activity to ganciclovir against TK– strains of HSV-1 and HSV-2. The higher cytotoxicity of prodrug compared to free ganciclovir in HEL cells (CC₅₀ = 135 μM vs. 230 μM) was attributed to the elaidic acid moiety. Compound and ganciclovir were similarly effective in inhibiting the replication of human cytomegalovirus (HCMV) and varicella-zoster virus (VZV) in HEL cells, with IC₅₀ values of 3.5-4.5 μM for the prodrug and 1.75-3.8 μM for ganciclovir. The *in vivo* antiviral efficacy of the prodrug was markedly better than that of ganciclovir against HSV-2 infections in mice; the prodrug reduced mortality of animals with intracerebral HSV-2 infection by 70-90% when given at doses of 10-40 mg/kg i.p., whereas ganciclovir showed no significant effect at doses of up to 20 mg/kg i.p.; complete protection against mortality was seen when ganciclovir and ganciclovir elaidic acid were given at equimolar oral doses of 80-160 and 160-320 mg/kg, respectively.

SOURCE – Norsk Hydro.

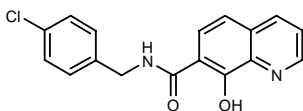
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2. Andrei, G. et al. *Antiviral activity of a novel compound P-4018 against different strains of herpes simplex virus in vitro and in vivo*. Antivir Res 1997, 34(2): Abst 119.
3. Andrei, G. et al. *Antiviral activity of ganciclovir elaidic acid ester against herpesviruses*. Antivir Res 2000, 45(3): 157.
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PNU-142796

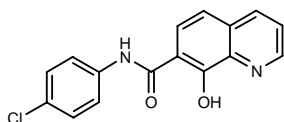
290721

N-(4-Chlorobenzyl)-8-hydroxyquinoline-7-carboxamide



C17 H13 Cl N2 O2; Mol wt: 312.7547

ACTION – Antiviral agent, an inhibitor of human cytomegalovirus (HCMV) DNA polymerase ($IC_{50} = 8.1 \mu M$). Another compound in this series of 8-hydroxyquinoline-7-carboxamides is:



PNU-144040 [290720]: C16 H11 Cl N2 O2

SOURCE – Pharmacia.

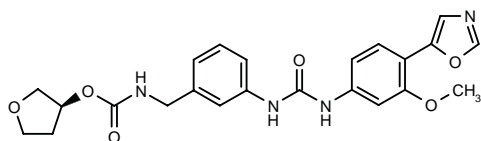
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VX-497

243628

N-[3-[3-[3-Methoxy-4-(5-oxazolyl)phenyl]ureido]benzyl]-carbamic acid tetrahydrofuran-3(S)-yl ester



C23 H24 N4 O6; Mol wt: 452.4646

ACTION – Potent, reversible, uncompetitive and orally active inhibitor of IMP dehydrogenase (IMPDH) active against a broad spectrum of DNA viruses such as hepatitis B virus (HBV), human cytomegalovirus (HCMV) and herpes simplex virus (HSV), and RNA viruses such as respiratory syncytial virus (RSV), parainfluenza-3 virus, bovine diarrhea virus, Venezuelan equine encephalomyelitis virus (VEE), dengue virus, yellow fever virus, coxsackie B3 virus and influenza A virus. Compound was 18-186-fold more potent than ribavirin against HBV, HCMV, RSV, HSV, parainfluenza-3 virus and VEE viral infections in cultured cells and its therapeutic index was 14- and 39-fold better than that of ribavirin against HBV and HCMV, respectively. In addition, compound potentiated the antiviral activity of interferon alfa against encephalomyocarditis virus and of purine nucleoside analogues against HIV-1 in MT-4 cells. It is orally bioavailable and was able to inhibit the primary antibody response to T- and B-cell mitogens in mice ($ED_{50} = 30 \text{ mg/kg p.o}$) and to prolong skin graft survival in mice.

Phase II clinical studies for the treatment of HCV infection were recently successfully concluded and a phase II clinical trial testing the tolerability and pharmacokinetic profile of VX-497 in patients with severe chronic psoriasis is planned. Potentially useful for the treatment of HCV and psoriasis, as well as for preventing organ transplant rejection and for the treatment of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease and systemic lupus erythematosus.

SOURCE – Vertex.

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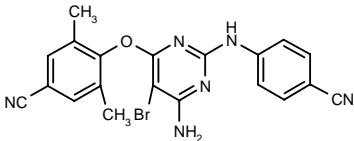
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AIDS MEDICINES

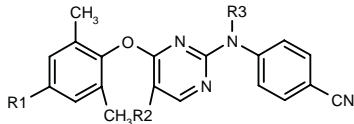
290137

4-[6-Amino-5-bromo-2-(4-cyanophenylamino)pyrimidin-4-yloxy]-3,5-dimethylbenzonitrile



C20 H15 Br N6 O; Mol wt: 435.2835

ACTION – Antiviral agent for AIDS with potent anti-HIV-1 activity in infected MT-4 cells (IC₅₀ = 0.002 μM) and low cytotoxicity in uninfected cells (CC₅₀ > 200 μM; selectivity index > 71,428). Compound is reported to be active against HIV-1 strains that have become resistant to known non-nucleoside reverse transcriptase inhibitors. It is also reported to have little or no binding affinity for human α₁-acid glycoprotein. Within this series of substituted pyrimidine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
290138	Me	Cl	H	C ₂₀ H ₁₇ ClN ₄ O
290139	Cl	Cl	H	C ₁₉ H ₁₄ Cl ₂ N ₄ O
290140	CN	Br	t-BuOCOCH2	C ₂₆ H ₂₄ BrN ₅ O ₃
290141	CN	Br	COCH2OCH2CO2Me	C ₂₅ H ₂₀ BrN ₅ O ₅

SOURCE – Janssen.

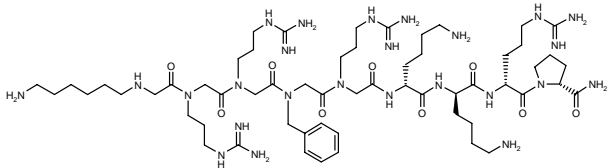
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CGP-64222*

246745

N-(6-Aminoethyl)glycyl-[N-(3-guanidinopropyl)]glycyl-[N-(3-guanidinopropyl)]glycyl-(N-benzyl)glycyl-[N-(3-guanidinopropyl)]glycyl-D-lysyl-D-lysyl-D-arginyl-D-prolinamide



C58 H107 N25 O9; Mol wt: 1298.6600

ACTION – Anti-HIV agent, a low-molecular-weight polycationic peptoid that specifically inhibits HIV Tat/transactivation response element complex formation at nanomolar concentrations, thereby inhibiting HIV-1 replication. Compound was able to inhibit the replication of a range of HIV-1 laboratory strains and clinical isolates including zidovudine-, DS-5000- and AR-177-resistant strains, as well as HIV-2 ROD (IC₅₀ = 1.8-14.5 μg/ml), but it was unable to suppress the replication of viruses resistant to bicyclam derivatives known to selectively interact with the chemokine CXCR4 receptor. Further investigations confirmed that the mechanism of action of CGP-64222 involves a selective interaction with the CXCR4 coreceptor, indicating that it blocks both early events in HIV-1 replication and viral entry into cells. CGP-64222 was devoid of cytotoxicity in MT-4 cells at concentrations up to 125 μg/ml.

SOURCE – Novartis.

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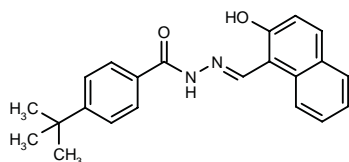
*Identified compound 246745 Drug Data Rep 1997, 019(06): 0543.

SP-1093V^{1,6,7,9,10}**290306**

Delivery formulation comprising the Fe(III) chelate of BBNH incorporated into a block copolymer

BBNH^{1-5,7-9}**290285**

4-*tert*-Butylbenzoic acid *N'*-(2-hydroxynaphthalen-1-yl-methylene)hydrazide



C22 H22 N2 O2 ; Mol wt: 346.4278

ACTION – Anti-HIV agent, an inhibitor of both HIV-1 DNA polymerase and HIV-1 reverse transcriptase ribonuclease H (RT RNase H). Compound consists of a formulation comprising the Fe(III) chelate of the insoluble active compound BBNH incorporated into a block copolymer in order to improve its aqueous solubility and cytotoxicity. It showed equivalent potency against HIV-1 and HIV-2 infection in MT-2 cells ($EC_{50} \sim 1 \mu M$) and retained activity against HIV-1 isolates resistant to both nucleoside and non-nucleoside reverse transcriptase inhibitors including nevirapine-, delavirdine- and efavirenz-resistant strains with multiple mutations. Treatment of HIV-1 chronically infected H9 cells with compound produced nascent virus with significantly reduced infectivity ($EC_{50} = 0.3 \mu M$), suggesting that compound may act by preventing or destabilizing reverse transcriptase dimerization during virus assembly and maturation, which represents a novel target for the development of new anti-HIV drugs. No induction of viral resistance was seen and preliminary single-dose toxicity studies indicate that it has low toxicity. Compound exhibited a long half-life in plasma and pharmacokinetic studies indicated that it crosses the blood–brain barrier.

SOURCES – McGill University, Montreal, PQ (CA); Supratek.

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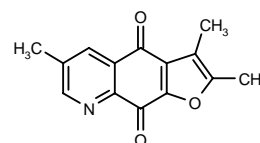
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TREATMENT OF PROTOZOAL DISEASES

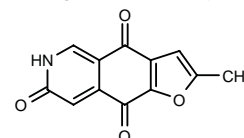
290176¹⁻³

2,3,6-Trimethylfuro[3,2-*g*]quinoline-4,9-dione



C14 H11 N O3; Mol wt: 241.2449

ACTION – Quinonic derivative with activity comparable to pyrimethamine against a virulent strain of *Toxoplasma gondii* (96.5% growth inhibition at 0.1 $\mu g/ml$). This and the compound shown below were selected for further testing *in vivo* in mice with *T. gondii* brain cysts.



290174³: C12 H7 N O4

SOURCE – Université Claude Bernard Lyon 1, Villeurbanne Cedex (FR).

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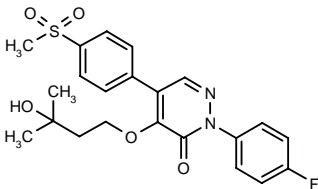
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2. Nebois, P. et al. *In vitro cytotoxic activity of naphtho[1,2-*b*]furan, furo[2,3-*f*]furo-[2,3-*g*]-and furo [3,2-*g*] quinoline derivatives*. Pharmazie 1999, 54(3): 215.
3. Nebois, P. et al. *Quinonic derivatives active against a virulent strain of Toxoplasma gondii. Synthesis of 2-methylfuro[2,3-*g*]- and [3,2-*g*]isoquinolinetriones*. Bioorg Med Chem Lett 2000, 10(9): 871.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

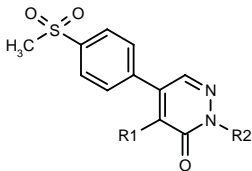
289625

2-(4-Fluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]pyridazin-3(2H)-one



C22 H23 F N2 O5 S; Mol wt: 446.4967

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor for the treatment of pain, fever, inflammation, rheumatoid arthritis, osteoarthritis, adhesions and cancer. The compound exhibited an IC₅₀ of 0.470 μM for inhibition of COX-2 and produced only 10% inhibition of COX-1 at 100 μM using cells expressing recombinant human enzymes. In human whole blood assays, IC₅₀ values for COX-2 and COX-1 inhibition were 0.47 and 29.12 μM, respectively. The compound showed a good pharmacokinetic profile with regard to once-daily dosing. Other exemplified pyridazinone compounds include the following:



Compound	R1	R2	Formula
289626	4-F-Ph	5-Cl-2-thienyl-CH2	C ₂₂ H ₁₆ ClFN ₂ O ₃ S ₂
289627	4-F-Ph	5-Me-2-thienyl	C ₂₂ H ₁₇ FN ₂ O ₃ S ₂
289628	i-BuCH2CH2O	4-F-Ph	C ₂₃ H ₂₅ FN ₂ O ₄ S
289629	i-BuCH2O	CH2CF3	C ₁₈ H ₂₁ F ₃ N ₂ O ₄ S
289733	i-PrCH=CHO	3-Cl-Ph	C ₂₂ H ₂₁ ClN ₂ O ₄ S

SOURCE – Abbott.

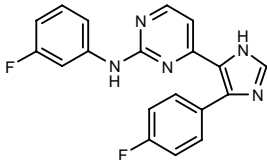
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289710

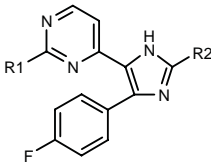
N-(3-Fluorophenyl)-4-[4-(4-fluorophenyl)-1H-imidazol-5-yl]pyrimidin-2-amine

N-(3-Fluorophenyl)-N-[4-[4-(4-fluorophenyl)-1H-imidazol-5-yl]pyrimidin-2-yl]amine

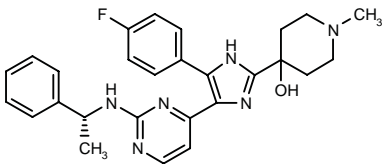


C19 H13 F2 N5; Mol wt: 349.3427

ACTION – Inhibitor of p38 MAP kinase that inhibits the production of cytokines such as TNF-α and IL-1 and is thus useful for the treatment of inflammatory and autoimmune diseases, e.g., rheumatoid arthritis. Other exemplified 4-phenyl-5-pyrimidinylimidazoles include the following:



Compound	R1	R2	Formula
289711	3-F-PhNH	t-Bu	C ₂₃ H ₂₁ F ₂ N ₅
289712	3-F-PhO	H	C ₁₉ H ₁₂ F ₂ N ₄ O
289713	(R)-NHCH(Me)Ph	1-NH2-cyclohexyl	C ₂₇ H ₂₉ FN ₆



289714: C27 H29 F N6 O

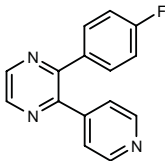
SOURCE – Novartis.

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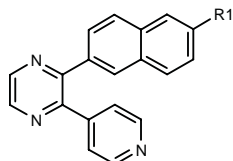
289765

2-(4-Fluorophenyl)-3-(4-pyridinyl)pyrazine



C15 H10 F N3; Mol wt: 251.2630

ACTION – CSBP/RK/p38 kinase inhibitor ($IC_{50} < 50 \mu M$) with the ability to inhibit the production of cytokines including IL-1, IL-6, IL-8 and TNF. It is useful for the treatment of cytokine-mediated disorders such as arthritic conditions, sepsis, septic shock, meningitis, ischemia, stroke, asthma, adult respiratory distress syndrome, osteoporosis, restenosis, reperfusion injury, diabetes, transplant rejection, inflammatory bowel disease, ulcerative colitis, etc. Other specifically claimed 4-pyridinyl and 4-pyrimidinyl substituted pyrazines are:



Compound	R1	Formula
289766	OMe	$C_{20}H_{15}N_3O$
289767	H	$C_{19}H_{13}N_3$

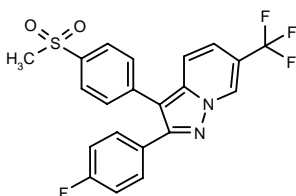
SOURCE – SmithKline Beecham.

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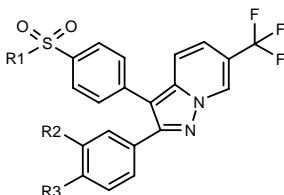
289786

2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrazolo[1,5-a]pyridine



C21 H14 F4 N2 O2 S; Mol wt: 434.4116

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor ($IC_{50} = 26 \text{ nM}$ and $> 100,000 \text{ nM}$ against COX-2 and COX-1, respectively, in COS cells) with potential utility in the treatment of pain, fever and inflammation. Other compounds from this series of pyrazolopyridine derivatives include the following:



Compound	R1	R2	R3	Formula
289787	NH2	F	H	$C_{20}H_{13}F_4N_3O_2S$
289788	Me	F	H	$C_{21}H_{14}F_4N_3O_2S$
289789	NH2	H	OEt	$C_{22}H_{18}F_3N_3O_3S$
289790	NH2	H	F	$C_{20}H_{13}F_4N_3O_2S$
289791	NH2	H	H	$C_{20}H_{14}F_3N_3O_2S$
289792	Me	H	H	$C_{21}H_{15}F_3N_3O_2S$

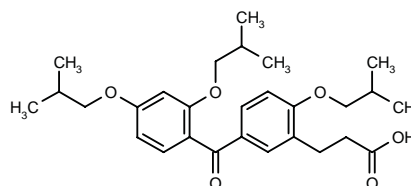
SOURCE – Glaxo Wellcome.

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289906

3-[5-(2,4-Diisobutoxybenzoyl)-2-isobutoxyphenyl]propionic acid



C28 H38 O6; Mol wt: 470.6022

ACTION – An inhibitor of the transcription factor AP-1 with potential in the treatment or prevention of diseases involving excessive expression of AP-1 such as rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Behcet's disease, polymyositis, glomerulonephritis, psoriasis, atherosclerosis, sepsis, diabetes, inflammatory bowel disease, encephalomyelitis, hepatitis, cancer, AIDS, Alzheimer's disease and ischemic disorders. *In vitro*, compound produced 24 and 90% inhibition of the binding of AP-1 to its recognition sequence at 200 and 500 μM , respectively, while *in vivo* it was active in a murine model of type II collagen-induced arthritis, producing 63% reduction in the arthritis score as compared to controls at 100 mg/kg/day p.o. x 2 weeks.

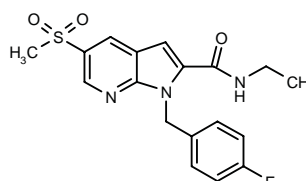
SOURCE – Toyama.

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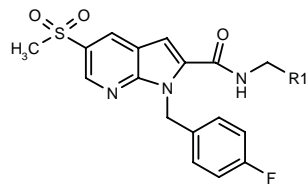
289909

N-Ethyl-1-(4-fluorobenzyl)-5-(methylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



C18 H18 F N3 O3 S; Mol wt: 375.4222

ACTION – Antiinflammatory agent, a potent and selective inhibitor of cyclooxygenase type 2 (COX-2; $IC_{50} = 0.2 \mu M$ vs. $> 20 \mu M$ for COX-1 in human whole blood). Within this series of indole derivatives, the following are also included:



Compound	R1	Formula
289910	H	C ₁₇ H ₁₆ FN ₃ O ₃ S
289911	Et	C ₁₉ H ₂₀ FN ₃ O ₃ S

SOURCE – Chugai.

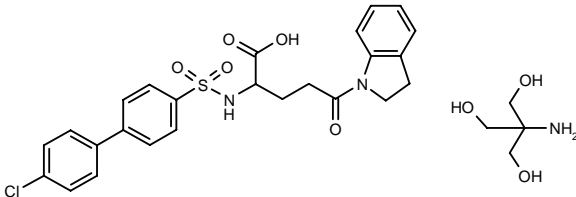
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1. Matsuoka, K. et al. (Chugai Pharmaceutical Co. Ltd.) *Indole derivs. having amide bond, and mono- or diazaindole derivs.* JP 2000136182.

289949

N-(4'-Chlorobiphenyl-4-ylsulfonyl)-5-(2,3-dihydro-1H-indol-1-yl)-5-oxo-DL-norvaline thromethamine salt

2-(4'-Chlorobiphenyl-4-ylsulfonamido)-5-(2,3-dihydro-1H-indol-1-yl)-5-oxopentanoic acid 2-hydroxy-1,1-bis(hydroxymethyl)ethylamine salt



C₂₅ H₂₃ Cl N₂ O₅ S . C₄ H₁₁ N O₃; Mol wt: 620.1196

ACTION – A representative compound from a series of N-arylsulfonyl-amino acid ω-amides that acts as a matrix metalloproteinases (MMPs) inhibitor, particularly active against human stromelysin (MMP-3) and human neutrophil collagenase (MMP-8; IC₅₀ = 0.1 and 0.01 μM, respectively). Solubility in water of the exemplified thromethamine salt was 58 mg/ml after 2 and 3 h, 600-fold higher than that of the corresponding free base. The compound may be useful in the treatment of osteoarthritis, rheumatoid arthritis, periodontal diseases and inflammatory diseases, among others.

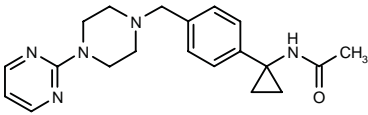
SOURCE – Aventis Pharma.

REFERENCES

1. Schwab, W. et al. (Aventis Pharma Deutschland GmbH) *N-Arylsulfonyl amino acid omega amides.* DE 19851184, WO 0027808.

290177

N-[1-[4-[4-(2-Pyrimidinyl)-1-piperazinylmethyl]phenyl]-cyclopropyl]acetamide



C₂₀ H₂₅ N₅ O; Mol wt: 351.4515

ACTION – Cytokine regulator that is able to suppress TNF-α production and enhance IL-10 production in lipopolysaccharide-stimulated mice. In rats with adjuvant-induced arthritis, compound given at doses of 3, 10 and 30 mg/kg/day p.o. for 5 days induced a dose-dependent reduction in inflammation in both hind paws.

SOURCE – Welfide.

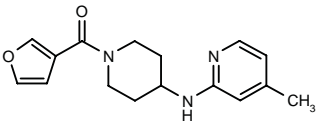
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1. Adachi, K. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Piperazine cpds. and medicinal use thereof.* EP 1029851, WO 9919301.

2. Hanano, T. et al. *Novel DMARDs on the basis of a new concept of dual cytokine regulation, TNF-α suppression and IL-10 augmentation.* Bioorg Med Chem Lett 2000, 10(9): 881.

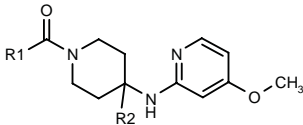
290238

1-(3-Furyl)-1-[4-(4-methylpyridin-2-ylamino)piperidin-1-yl]methanone



C₁₆ H₁₉ N₃ O₂; Mol wt: 285.3451

ACTION – Inducible nitric oxide synthase (iNOS) inhibitor with potential in the treatment or prevention of pain and inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis and osteoarthritis. Other specifically claimed compounds from this series of 2-aminopyridine derivatives include the following:



Compound	R1	R2	Formula
290239	2-thienyl	H	C ₁₆ H ₁₃ N ₃ O ₂ S
290240	5-Br-2-thienyl	H	C ₁₆ H ₁₃ BrN ₃ O ₂ S
290241	3,5-(Br)2-Ph	H	C ₁₈ H ₁₃ Br ₂ N ₃ O ₂
290242	5-Me-1-Ph-4-pyrazolyl	H	C ₂₂ H ₂₅ N ₅ O ₂
290243	4-I-Ph	H	C ₁₈ H ₂₀ IN ₃ O ₂
290244	3-isoxazolyl	H	C ₁₅ H ₁₈ N ₄ O ₃
290245	4-Cl-Ph	Me	C ₁₉ H ₂₂ ClN ₃ O ₂

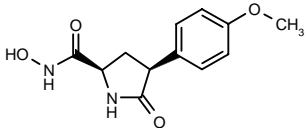
SOURCE – AstraZeneca.

REFERENCES

1. Cook, A. et al. (AstraZeneca UK, Ltd.; AstraZeneca AB) *Compounds*. WO 0027842.

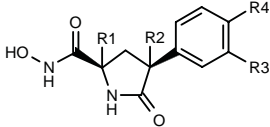
290256

4(*S*)-(4-Methoxyphenyl)-5-oxopyrrolidine-2(*R*)-carbohydroxamic acid

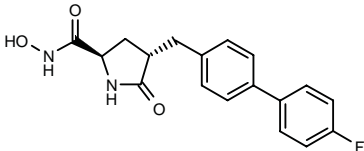


C12 H14 N2 O4; Mol wt: 250.2526

ACTION – Matrix metalloproteinase (MMP) inhibitor that selectively inhibits MMP-13 (collagenase 3) and/or TNF- α -converting enzyme (TACE) with respect to MMP-1 (fibroblast collagenase); it is at least 100-fold less potent against recombinant human MMP-1 than against TACE. Potentially useful in the treatment of a wide variety of disorders including osteoarthritis and rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, Alzheimer’s disease, restenosis, osteoporosis, atherosclerosis, stroke and cancer. Other specifically claimed compounds from this series of 5-oxo-pyrrolidine-2-carboxylic acid hydroxamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
290257	H	H	H	OPh	C ₁₇ H ₁₆ N ₂ O ₄
290258	H	H	4-Cl-PhO	H	C ₁₇ H ₁₅ ClN ₂ O ₄
290259	H	H	H	Ph	C ₁₇ H ₁₆ N ₂ O ₃
290260	H	H	H	OCH2Ph	C ₁₈ H ₁₈ N ₂ O ₄
290261	H	H	H	3,5-(F)2-PhCH2O	C ₁₈ H ₁₆ F ₂ N ₂ O ₄
290263	H	Me	H	4-F-PhO	C ₁₈ H ₁₇ FN ₂ O ₄
290264	Me	Me	H	4-Cl-PhO	C ₁₉ H ₁₉ ClN ₂ O ₄



290262: C18 H17 F N2 O3

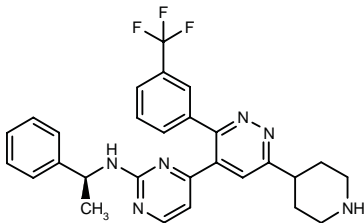
SOURCE – Pfizer.

REFERENCES

1. Laird, E.R. and Robinson, R.P. Jr. (Pfizer Products Inc.) *5-Oxo-pyrrolidine-2-carboxylic acid hydroxamide derivs*. EP 1004578, JP 2000143625, US 6114361.

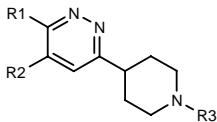
290509

N-[1(*S*)-Phenylethyl]-*N*-[4-[6-(4-piperidiny)-3-[3-(trifluoromethyl)phenyl]pyridazin-4-yl]pyrimidin-2-yl]amine

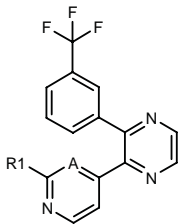


C28 H27 F3 N6; Mol wt: 504.5573

ACTION – Cytokine inhibitor that is particularly active against the production or activity of IL-1, IL-6, IL-8 and TNF, expected to be useful for the treatment of rheumatoid arthritis, osteoarthritis, osteoporosis, Crohn’s disease, as well as other cytokine-mediated disorders. Other specifically claimed substituted heterocyclic compounds are:



Compound	R1	R2	R3	Formula
290511	3-CF3-Ph	(<i>S</i>)-2-[PhCH(Me)-NH]-4-pyrimidinyl	Me	C ₂₉ H ₂₉ F ₃ N ₆
290512	3-CF3-Ph	4-Pyr	Me	C ₂₂ H ₂₁ F ₃ N ₄
290514	3-CF3-Ph	4-Pyr	H	C ₂₁ H ₁₉ F ₃ N ₄
290515	3-CF3-Ph	(<i>S</i>)-2-[PhCH(Me)-NH]-4-Pyr	H	C ₂₉ H ₂₈ F ₃ N ₅
290516	3-CF3-Ph	(<i>S</i>)-2-[PhCH(Me)-NH]-4-Pyr	Me	C ₃₀ H ₃₀ F ₃ N ₅
290520	(<i>S</i>)-2-[PhCH(Me)NH]-4-pyrimidinyl	3-CF3-Ph	H	C ₂₈ H ₂₇ F ₃ N ₆
290521	(<i>S</i>)-2-[PhCH(Me)NH]-4-pyrimidinyl	3-CF3-Ph	Me	C ₂₉ H ₂₉ F ₃ N ₆
290522	4-Pyr	3-CF3-Ph	H	C ₂₁ H ₁₉ F ₃ N ₄



Compound	R1	A	Formula
290517	(<i>S</i>)-NHCH(Me)Ph	N	C ₂₃ H ₁₈ F ₃ N ₅
290518	(<i>S</i>)-NHCH(Me)Ph	CH	C ₂₄ H ₁₉ F ₃ N ₄
290519	H	CH	C ₁₆ H ₁₀ F ₃ N ₃

SOURCE – Merck & Co.

REFERENCES

1. Claremon, D.A. and Ponticello, G.S. (Merck & Co., Inc.) *Cpds. having cytokine inhibitory activity*. WO 0031065.

Ad5E1mIL-4

269726

Recombinant human replication-deficient type 5 adenovirus (Ad5E1) expressing murine interleukin-4 (mIL-4)

ACTION – Interleukin-4 (IL-4) gene therapy for the treatment of rheumatoid arthritis that provides local overexpression of IL-4 via a recombinant replication-deficient human type 5 adenovirus vector. In mice with collagen-induced arthritis, the therapy prevented joint damage and bone erosion in the knees, as well as the formation of osteoclast-like cells, as demonstrated by the decrease in tartrate-resistant acid phosphatase activity. *In vitro* studies on bone samples from arthritic patients indicated that IL-4 induced consistent suppression of type I collagen breakdown and enhanced the synthesis of type I procollagen, indicating that it promotes tissue repair.

SOURCES – McMaster University, Hamilton, ON (CA); University of Nijmegen, Nijmegen (NL).

REFERENCES

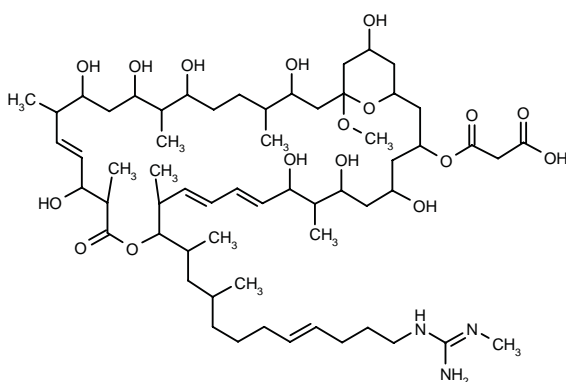
1. Lubberts, E. et al. *IL-4 gene therapy for collagen arthritis suppresses synovial IL-17 and osteoprotegerin ligand and prevents bone erosion*. J Clin Invest 2000, 105(12): 1697.

2. Lubberts, E. et al. *Protection against cartilage damage and bone-erosion in collagen-induced arthritis by local adenoviral vector-mediated interleukin-4 expression in the mouse knee joint*. 9th Int Conf Inflamm Res Assoc (Nov 1-5, Hershey) 1998, Abstr W3b.

AZAROMYCIN SC

289793

Malonic acid [5,7,9,19,23,25,27,31,35-nonahydroxy-33-methoxy-8,14,18,22,26,30-hexamethyl-15-[11-(*N*²-methylguanidino)-1,3-dimethyl-7(*E*)-undecenyl]-17-oxo-16,37-dioxabicyclo[31.3.1]heptatriaconta-10,12,20-trien-3-yl] monoester



C60 H105 N3 O17; Mol wt: 1140.4940

ACTION – Antiinflammatory compound obtained from the fungus SCRC89 (FERM P-16959). The compound was found to inhibit cytoplasmic phospholipase A₂ (cPLA₂), exhibiting an IC₅₀ value of 3.0 µg/ml against cPLA₂ from rabbit platelets.

SOURCE – Sagami.

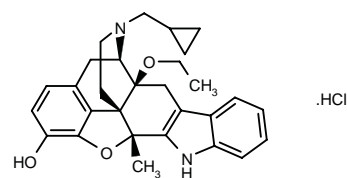
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1. Yazawa, K. et al. (Sagami Chemical Research Center) *Azaromycin SC group, and cytoplasm phospholipase A₂ inhibitors*. JP 2000119292.

HS-378*

231322

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-14-ethoxy-3-hydroxy-5-methylindolo[2',3':6,7]morphinan hydrochloride



C29 H32 N2 O3 . HCl; Mol wt: 493.0437

ACTION – High-affinity delta opioid (DOP) receptor ligand ($K_i = 0.78$ nM) with high selectivity over mu (MOP) and kappa (KOP) subtypes ($K_i = 38.7$ and 59.2 nM, respectively). In an *in vitro* functional test on mouse vas deferens, compound exhibited antagonist activity, being about 10 times less potent than naltrindole but much more selective. *In vivo*, it exhibited antiinflammatory activity in adjuvant-induced arthritis in rats, where at doses of 0.5-8 mg/kg i.v.) it produced a significant reduction in the clinical severity of inflammation, with reductions in paw swelling and osteoclast number in the ankle joint. Potentially useful for the treatment of inflammatory arthritic diseases.

SOURCE – AstraZeneca.

REFERENCES

1. Schmidhammer, H. (Astra AB) *New antagonist cpds*. EP 0759922, JP 1998500131, WO 9531463.

2. Krassing, R. et al. *A novel method for the introduction of a 5-β-methyl group into 4,5-α-epoxymorphinan-6-ones via the enol ether*. Helv Chim Acta 2000, 83(2): 380.

3. Schmidhammer, H. et al. *Synthesis and biological evaluation of 14-alkoxymorphinans. 14. 14-Ethoxy-5-methyl substituted indolomorphinans with δ opioid receptor selectivity*. Bioorg Med Chem Lett 1997, 7(2): 151.

4. Schmidhammer, H. et al. *Synthesis and biological evaluation of 14-alkoxymorphinans. Part 15. Novel δ opioid receptor antagonists with high affinity and selectivity in the 14-alkoxy-substituted indolomorphinan series*. Helv Chim Acta 1998, 81(6): 1064.

5. Spetea, M. et al. *Anti-arthritis effects of the δ-selective opioid antagonist HS 378*. Ann Rheum Dis 2000, 59(Suppl. 1): Abstr POS-434.

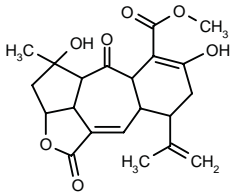
6. Spetea, M. et al. *Anti-inflammatory effect of the δ-selective opioid antagonist HS 378 in adjuvant arthritis*. 3rd Eur Opioid Conf (April 9-11, Guildford) 2000, Abstr T9.

*Identified compound **231322** Drug Data Report 1996, 018(03): 0270.

RAMESWARALIDE

289908

4,7-Dihydroxy-4-methyl-9-(1-methylvinyl)-1,5-dioxo-2a,3,4,4a,5,5a,8,9,9a,10b-decahydro-1*H*-benzo[5,6]-azuleno[1,8-*bc*]furan-6-carboxylic acid methyl ester



C21 H24 O7; Mol wt: 388.4136

ACTION – Antiinflammatory agent isolated from an extract of the soft coral *Sinularia dissecta*, with potential in the treatment of arthritis, psoriasis and inflammatory bowel disease.

SOURCE – University of California, Oakland, CA (US).

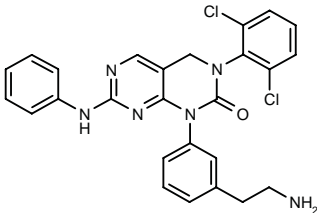
REFERENCES

1. Faulkner, J.D. and Venkateswarlu, Y. (University of California, Oakland) *Rameswaralide and rameswaralide derivs.* WO 0027839.

IMMUNOMODULATING DRUGS

289507

1-[3-(2-Aminoethyl)phenyl]-3-(2,6-dichlorophenyl)-7-(phenylamino)-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidin-2-one



C26 H22 Cl2 N6 O; Mol wt: 505.4068

ACTION – An inhibitor of protein kinases, especially the T-cell tyrosine kinase p56^{lck} (IC₅₀ = 0.03 nM against human recombinant enzyme), with potential in the treatment or prophylaxis of inflammatory, immunological, oncological, bronchopulmonary, dermatological and cardiovascular disorders, in the treatment of asthma, CNS disorders or diabetic complications, or for the prevention of transplant rejection. A specifically claimed compound from a series of amino-substituted dihydropyrimido[4,5-*d*]pyrimidinones.

SOURCE – Roche.

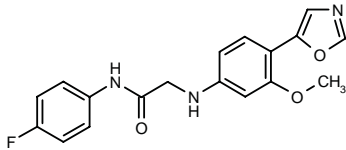
REFERENCES

1. Harris, W. et al. (F. Hoffmann-La Roche AG) *Bicyclic nitrogen heterocycles.* WO 0024744.

289773

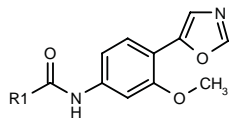
N-(4-Fluorophenyl)-2-[3-methoxy-4-(5-oxazolyl)phenyl-amino]acetamide

*N*¹-(4-Fluorophenyl)-*N*²-[3-methoxy-4-(5-oxazolyl)-phenyl]glycinamide



C18 H16 F N3 O3; Mol wt: 341.3404

ACTION – IMP dehydrogenase (IMPDH) inhibitor for the treatment of transplant rejection, autoimmune and inflammatory diseases, cancer, reperfusion injury, proliferative disorders and DNA or RNA viral diseases. Other specifically claimed compounds include the following:



Compound	R1	Formula
289775	3-[3(S)-THF-OCONHCH2]-PhNHCOCH2	C ₂₅ H ₂₆ N ₄ O ₇
289777	CONHC(Me)2CH(OH)Pr	C ₁₉ H ₂₅ N ₃ O ₅
289779	4-F-PhCH2C(Me)2NHCO	C ₂₂ H ₂₂ FN ₃ O ₄
289780	1-ethynyl-cyclohexyl-NHCO	C ₂₀ H ₂₁ N ₃ O ₄
289782	5-Me-2-thienyl	C ₁₆ H ₁₄ N ₂ O ₃ S
289784	2,3-(MeO)2-PhCH=CH	C ₂₁ H ₂₀ N ₂ O ₅
289785	2,4-(Me)2-5-thiazolyl	C ₁₆ H ₁₅ N ₃ O ₃ S

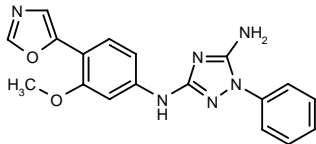
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Gu, H.H. et al. (Bristol-Myers Squibb Co.) *Novel inhibitors of IMPDH enzyme.* WO 0026197.

289801

*N*³-[3-Methoxy-4-(5-oxazolyl)phenyl]-1-phenyl-1*H*-1,2,4-triazole-3,5-diamine



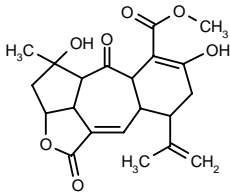
C18 H16 N6 O2; Mol wt: 348.3644

ACTION – IMP dehydrogenase (IMPDH) inhibitor for the treatment of transplant rejection, autoimmune and inflammatory diseases, cancer, reperfusion injury, proliferative disorders and DNA or RNA viral diseases. Other specifically claimed compounds include the following:

RAMESWARALIDE

289908

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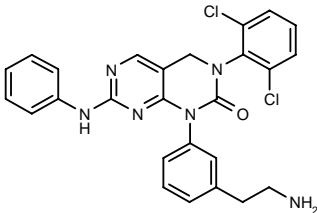
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IMMUNOMODULATING DRUGS

289507

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SOURCE – Roche.

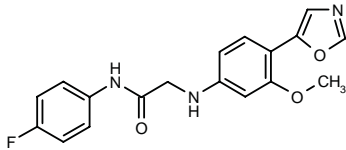
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289773

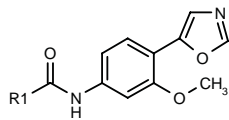
N-(4-Fluorophenyl)-2-[3-methoxy-4-(5-oxazolyl)phenyl-amino]acetamide

*N*¹-(4-Fluorophenyl)-*N*²-[3-methoxy-4-(5-oxazolyl)-phenyl]glycinamide



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289779	4-F-PhCH2C(Me)2NHCO	C ₂₂ H ₂₂ FN ₃ O ₄
289780	1-ethynyl-cyclohexyl-NHCO	C ₂₀ H ₂₁ N ₃ O ₄
289782	5-Me-2-thienyl	C ₁₆ H ₁₄ N ₂ O ₃ S
289784	2,3-(MeO)2-PhCH=CH	C ₂₁ H ₂₀ N ₂ O ₅
289785	2,4-(Me)2-5-thiazolyl	C ₁₆ H ₁₅ N ₃ O ₃ S

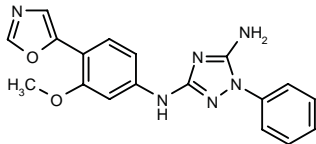
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Gu, H.H. et al. (Bristol-Myers Squibb Co.) *Novel inhibitors of IMPDH enzyme.* WO 0026197.

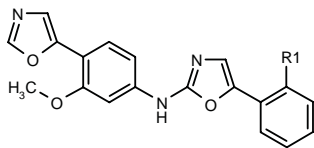
289801

*N*³-[3-Methoxy-4-(5-oxazolyl)phenyl]-1-phenyl-1*H*-1,2,4-triazole-3,5-diamine

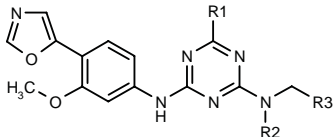


C18 H16 N6 O2; Mol wt: 348.3644

ACTION – IMP dehydrogenase (IMPDH) inhibitor for the treatment of transplant rejection, autoimmune and inflammatory diseases, cancer, reperfusion injury, proliferative disorders and DNA or RNA viral diseases. Other specifically claimed compounds include the following:



Compound	R1	Formula
289805	NHAc	C ₂₁ H ₁₈ N ₄ O ₄
289806	CONHMe	C ₂₁ H ₁₈ N ₄ O ₄
289812	1-Et-3-pyrrolidinyl-CH ₂ NHCOCH ₂	C ₂₈ H ₃₁ N ₅ O ₄



Compound	R1	R2	R3	Formula
289807	H	H	i-Bu	C ₁₈ H ₂₂ N ₆ O ₂
289810	Ph	CH ₂ Ph	H	C ₂₇ H ₂₄ N ₆ O ₂

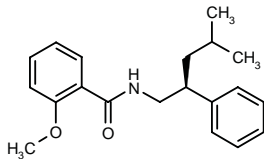
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Liu, C. et al. (Bristol-Myers Squibb Co.) *Cpds. derived from an amine nucleus that are inhibitors of IMPDH enzyme.* WO 0025780.

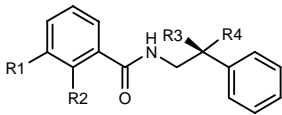
289822

2-Methoxy-*N*-[4-methyl-2(*S*)-phenylpentyl]benzamide



C₂₀ H₂₅ N O₂; Mol wt: 311.4225

ACTION – Potassium channel blocker that inhibits the voltage-gated potassium channels Kv1.3 and Kv1.5 and is therefore expected to be of use in the treatment of autoimmune diseases, for the prevention of transplant rejection and in the therapy of atrial arrhythmias. Other specifically claimed benzamide derivatives are:



Compound	R1	R2	R3	R4	Formula
289823	H	OMe	allyl-OCOO(CH ₂) ₃	H	C ₂₃ H ₂₇ NO ₅
289824	H	OMe	Et	Et	C ₂₀ H ₂₅ NO ₂
289825	-CH ₂ CH ₂ O-		Et	Et	C ₂₁ H ₂₅ NO ₂
289826	H	OMe	(CH ₂) ₃ OH	H	C ₁₉ H ₂₃ NO ₃

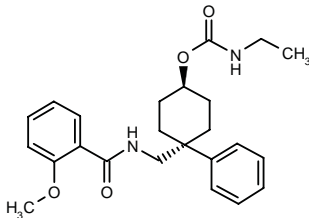
SOURCE – Merck & Co.

REFERENCES

1. Baker, R.K. et al. (Merck & Co., Inc.) *Benzamide potassium channel inhibitors.* WO 0025774.

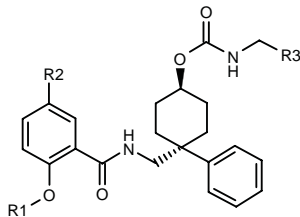
289827

N-Ethylcarbamic acid *trans*-4-(2-methoxybenzamido-amidomethyl)-4-phenylcyclohexyl ester



C₂₄ H₃₀ N₂ O₄; Mol wt: 410.5110

ACTION – Potassium channel blocker that inhibits the voltage-gated potassium channels Kv1.3 and Kv1.5 and is therefore expected to be of use in the treatment of autoimmune diseases, for the prevention of transplant rejection and in the therapy of atrial arrhythmias. Other specifically claimed carbocyclic compounds are:



Compound	R1	R2	R3	Formula
289828	H	F	vinyl	C ₂₄ H ₂₇ FN ₂ O ₄
289829	Me	H	Et	C ₂₅ H ₃₂ N ₂ O ₄
289830	Me	H	H	C ₂₃ H ₂₈ N ₂ O ₄
289831	Me	H	vinyl	C ₂₅ H ₃₀ N ₂ O ₄

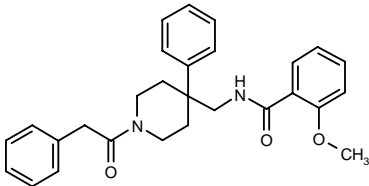
SOURCE – Merck & Co.

REFERENCES

1. Baker, R.K. et al. (Merck & Co., Inc.) *Carbocyclic potassium channel inhibitors.* WO 0025770.

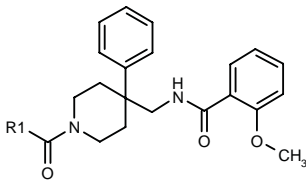
289865

2-Methoxy-*N*-[4-phenyl-1-(2-phenylacetyl)piperidin-4-yl-methyl]benzamide



C₂₈ H₃₀ N₂ O₃; Mol wt: 442.5560

ACTION – Potassium channel blocker that inhibits the voltage-gated potassium channels Kv1.3 and Kv1.5. Based on its Kv1.3-inhibitory activity, the compound is expected to be useful as an immunosuppressant, and its Kv1.5-inhibitory properties make it potentially useful as an antiarrhythmic agent. Other specifically claimed heterocyclic compounds are:



Compound	R1	Formula
289866	NHEt	C ₂₃ H ₂₉ N ₃ O ₃
289867	CH ₂ CH ₂ Ph	C ₂₉ H ₃₂ N ₂ O ₃

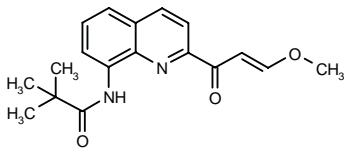
SOURCE – Merck & Co.

REFERENCES

1. Bao, J. et al. (Merck & Co., Inc.) *Heterocyclic potassium channel inhibitors*. WO 0025786.

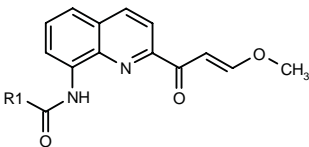
289915

N-[2-[3-Methoxy-2(E)-propenoyl]quinolin-8-yl]-2,2-dimethylpropionamide



C18 H20 N2 O3; Mol wt: 312.3670

ACTION – Immunosuppressive and antibacterial agent proven to inhibit T-cell proliferation in a murine mixed lymphocyte reaction (IC₅₀ = 3.8 μM). Other compounds from this series of 2-acylquinoline derivatives include the following:



Compound	R1	Formula
289916	Me	C ₁₅ H ₁₄ N ₂ O ₃
289917	allyl-O	C ₁₇ H ₁₆ N ₂ O ₄

SOURCE – Kyowa Hakko.

REFERENCES

1. Akama, T. et al. (Kyowa Hakko Kogyo Co., Ltd.) *2-Acylquinoline derivs*. JP 2000128866.

290160

Immunotoxin comprising an antibody specific to human CD86 coupled with the toxin gelonin

ACTION – Immunotoxin specific for CD86-expressing cells comprising an antibody specific to human CD86 coupled to the toxin gelonin that selectively binds to and kills CD86-expressing cells. *In vitro*, compound was shown to inhibit the growth of CD86-positive L540, L428, KM-H2 and Raji tumor cell lines in a concentration-dependent manner. Potentially useful for the treatment of immune diseases, particularly for preventing allograft rejection and for treating autoimmune diseases and various malignancies of lymphoid origin.

SOURCE – Innogenetics.

REFERENCES

1. De Boer, M. and De Gast, G. (Innogenetics NV) *Immunotoxins specific for CD86 expressing cells*. US 6071519, WO 9640260.

290303

H-L-Cys-L-Met-L-Tyr-Gly-Gly-L-Val-L-Thr-L-Glu-L-His-L-Glu-Gly-L-Asn-L-Lys-L-Lys-L-Asn-L-Val-L-Thr-L-Val-L-Gln-L-Glu-L-Leu-L-Asp-L-Tyr-L-Lys-L-Ile-L-Arg-L-Lys-L-Tyr-L-Leu-L-Val-L-Asp-L-Asn-L-Lys-L-Lys-L-Leu-L-Tyr-Gly-L-Cys-OH

C195 H311 N53 O59 S3; Mol wt: 4438.1120

ACTION – Peptide derived from homologous sequences of the family of staphylococcal and streptococcal pyrogenic toxins, potentially useful for eliciting an immunogenic response including protection against toxic shock syndrome, as well as for use in diagnostic assays. The peptide was shown to induce significant antibody titers in rabbits, as well as to inhibit the blastogenesis of human peripheral blood mononuclear cells (PBMCs) in response to several staphylococcal and streptococcal toxins. In addition, the administration of antibodies against this peptide prevented severe toxic shock in rabbits challenged with the toxins SEB and NRS.

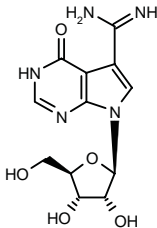
SOURCE – Rockefeller University, New York, NY (US).

REFERENCES

1. Bannan, J.D. and Zabriskie, J.B. (Rockefeller University) *Peptides useful for reducing symptoms of toxic shock syndrome*. US 6075119.

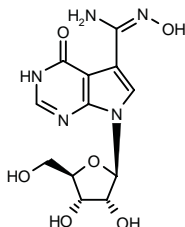
291177

4-Oxo-7-(β-D-ribofuranosyl)-4,7-dihydro-3H-pyrrolo-[2,3-d]pyrimidine-5-carboxamide



C12 H15 N5 O5; Mol wt: 309.2805

ACTION – Cytokine modulator able to enhance the production of type 2 cytokines, in particular IL-4 (> 200%) and IL-5 (36%), and to suppress type 1 cytokines including interferon gamma (30%), IL-2 (35%) and TNF- α (26%), in activated human T-cells. Potentially useful for the treatment of diseases associated with cytokine type 1 responses including autoimmune diseases such as multiple sclerosis and rheumatoid arthritis. Another representative compound within this series of pyrrolo-[2,3-*d*]-4-pyrimidone nucleosides is:



291178: C12 H15 N5 O6

SOURCE – ICN.

REFERENCES

1. Wang, G. et al. *Synthesis and cytokine modulation properties of pyrrolo[2,3-*d*]-4-pyrimidone nucleosides*. J Med Chem 2000, 43(13): 2566.

HuZAF

291250

Humanized monoclonal antibody to interferon gamma

ACTION – Humanized monoclonal antibody that binds to and neutralizes interferon gamma and is thus useful for the treatment of immune disorders, particularly autoimmune diseases.

SOURCE – Protein Design Labs.

REFERENCES

1. Vasquez, M. et al. (Protein Design Labs, Inc.) *Humanized antibodies to γ -interferon*. WO 0032634.

HZ4B4-1

291131

Humanized antibody that specifically binds the human protein 4-1BB

ACTION – Humanized monoclonal antibody obtained from the mouse monoclonal antibody 4B4-1-1 that specifically binds the human protein 4-1BB. This antibody is useful as an immunosuppressant and for the treatment of autoimmune diseases, being specifically claimed for the therapy of rheumatoid arthritis and transplant rejection. Another antibody obtained from 4B4-1-1 is:

HZ4B4-2 [291132]

SOURCE – LG Chem.

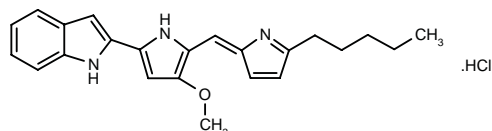
REFERENCES

1. Hong, H.J. et al. (LG Chem Ltd.) *Humanized antibody specific for human 4-1BB and pharmaceutical compsn. comprising same*. WO 0029445.

PNU-190192

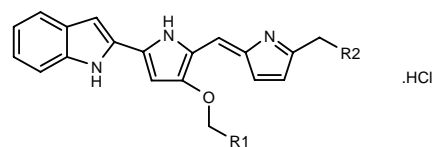
290212

2-[4-Methoxy-5-(5-pentyl-2*H*-pyrrol-2-ylidenemethyl)-1*H*-pyrrol-2-yl]-1*H*-indole hydrochloride



C23 H25 N3 O . HCl; Mol wt: 395.9314

ACTION – Immunosuppressive agent with good oral bioavailability, also reported to be useful for the treatment of adult T-cell leukemia-lymphoma by virtue of its ability to inhibit IL-2-induced activation and expansion of murine and human T-cells. Compound was proven active in a delayed-type hypersensitivity (DTH) test in mice (ED₃₀ = 7.1 mg/kg p.o.) and exhibited good oral bioavailability (38% in rats at 10 mg/kg p.o.). In addition, it was found to inhibit IL-2-induced proliferation of Th2 murine D10-G4.1 cells by 52 and 98%, respectively, at 30 and 100 ng/ml. Other exemplified compounds from this series of indolyl-pyrrolidenemethylpyrrole derivatives include the following:



Compound	R1	R2	Formula
PNU-190364 [290214]	H	H	C ₁₉ H ₁₇ N ₃ O.HCl
PNU-190537 [290216]	Ph	H	C ₂₅ H ₂₁ N ₃ O.HCl
PNU-166823 [290218]	H	C10H21	C ₂₉ H ₃₇ N ₃ O.HCl

SOURCE – Pharmacia.

REFERENCES

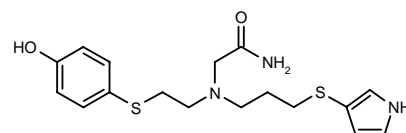
1. D'Alessio, R. et al. (Pharmacia & Upjohn SpA) *Indolyl-pyrrolydenemethylpyrrole derivs. and process for their preparation*. US 6071947, WO 9840380.

ONCOLYTIC DRUGS

ANTIMETABOLITES

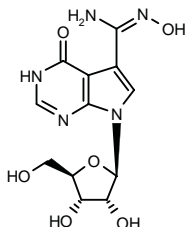
290265

2-[*N*-[2-(4-Hydroxyphenyl)sulfanyl]ethyl]-*N*-[3-(1*H*-pyrrol-3-ylsulfanyl)propyl]amino]acetamide



C17 H23 N3 O2 S2; Mol wt: 365.5197

ACTION – Cytokine modulator able to enhance the production of type 2 cytokines, in particular IL-4 (> 200%) and IL-5 (36%), and to suppress type 1 cytokines including interferon gamma (30%), IL-2 (35%) and TNF- α (26%), in activated human T-cells. Potentially useful for the treatment of diseases associated with cytokine type 1 responses including autoimmune diseases such as multiple sclerosis and rheumatoid arthritis. Another representative compound within this series of pyrrolo-[2,3-*d*]-4-pyrimidone nucleosides is:



291178: C12 H15 N5 O6

SOURCE – ICN.

REFERENCES

1. Wang, G. et al. *Synthesis and cytokine modulation properties of pyrrolo[2,3-*d*]-4-pyrimidone nucleosides*. J Med Chem 2000, 43(13): 2566.

HuZAF

291250

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HZ4B4-2 [291132]

SOURCE – LG Chem.

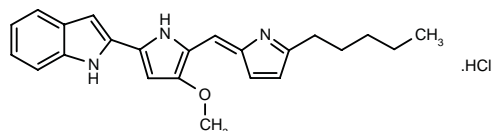
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PNU-190192

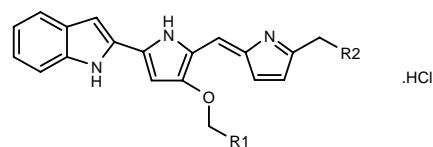
290212

2-[4-Methoxy-5-(5-pentyl-2*H*-pyrrol-2-ylidenemethyl)-1*H*-pyrrol-2-yl]-1*H*-indole hydrochloride



C23 H25 N3 O . HCl; Mol wt: 395.9314

ACTION – Immunosuppressive agent with good oral bioavailability, also reported to be useful for the treatment of adult T-cell leukemia-lymphoma by virtue of its ability to inhibit IL-2-induced activation and expansion of murine and human T-cells. Compound was proven active in a delayed-type hypersensitivity (DTH) test in mice (ED₃₀ = 7.1 mg/kg p.o.) and exhibited good oral bioavailability (38% in rats at 10 mg/kg p.o.). In addition, it was found to inhibit IL-2-induced proliferation of Th2 murine D10-G4.1 cells by 52 and 98%, respectively, at 30 and 100 ng/ml. Other exemplified compounds from this series of indolyl-pyrrolidenemethylpyrrole derivatives include the following:



Compound	R1	R2	Formula
PNU-190364 [290214]	H	H	C ₁₉ H ₁₇ N ₃ O.HCl
PNU-190537 [290216]	Ph	H	C ₂₅ H ₂₁ N ₃ O.HCl
PNU-166823 [290218]	H	C10H21	C ₂₉ H ₃₇ N ₃ O.HCl

SOURCE – Pharmacia.

REFERENCES

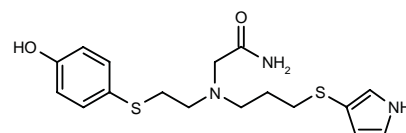
1. D'Alessio, R. et al. (Pharmacia & Upjohn SpA) *Indolyl-pyrrolydenemethylpyrrole derivs. and process for their preparation*. US 6071947, WO 9840380.

ONCOLYTIC DRUGS

ANTIMETABOLITES

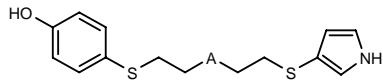
290265

2-[*N*-[2-(4-Hydroxyphenyl)sulfanyl]ethyl]-*N*-[3-(1*H*-pyrrol-3-ylsulfanyl)propyl]amino]acetamide



C17 H23 N3 O2 S2; Mol wt: 365.5197

ACTION – Antineoplastic agent that suppresses the proliferation of cancer cells selectively by virtue of its ribonucleotide reductase-inhibitory activity (IC₅₀ = 0.41 μM against purified human enzyme). Compound was shown to inhibit the proliferation of HeLa S3 cells with an IC₅₀ value of 0.61 μM. A representative compound from a series of heteroarylthio derivatives, wherein the following are also included:



Compound	A	Formula
290266	-O-	C ₁₄ H ₁₇ NO ₂ S ₂
290267	-N(CH ₂ CONH ₂)-	C ₁₆ H ₂₁ N ₃ O ₂ S ₂
290268	-CH ₂ N(CH ₂ CONH ₂)-	C ₁₇ H ₂₃ N ₃ O ₂ S ₂
290269	-CH ₂ N(CH ₂ CONH ₂)CH ₂ -	C ₁₈ H ₂₅ N ₃ O ₂ S ₂

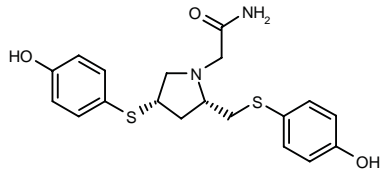
SOURCES – Fuji Photo Film; Kyowa Hakko.

REFERENCES

1. Tamaoki, T. et al. (Kyowa Hakko Kogyo Co., Ltd.;Fuji Photo Film Co., Ltd.) *Heteroarylthio cpds. and cancer remedies containing the same*. WO 0029376.

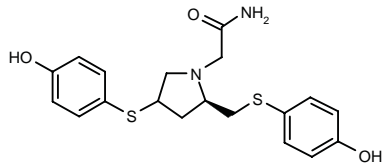
290270

2-[4(S)-(4-Hydroxyphenylsulfanyl)-2(S)-(4-hydroxyphenyl-sulfanylmethyl)pyrrolidin-1-yl]acetamide

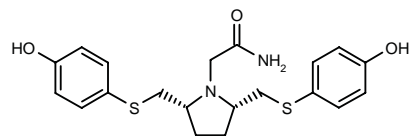


C19 H22 N2 O3 S2; Mol wt: 390.5258

ACTION – Antineoplastic agent that selectively suppresses the proliferation of cancer cells by virtue of its ribonucleotide reductase-inhibitory activity (IC₅₀ = 1.01 μM against purified human enzyme). Compound was shown to inhibit the proliferation of HeLa S3 cells with an IC₅₀ value of 1.25 μM. A representative compound from a series of bisaryl derivatives, wherein the following are also included:



Compound	Isomer	Formula
290272	S	C ₁₉ H ₂₂ N ₂ O ₃ S ₂
290273	R	C ₁₉ H ₂₂ N ₂ O ₃ S ₂



290271: C20 H24 N2 O3 S2

SOURCES – Fuji Photo Film; Kyowa Hakko.

REFERENCES

1. Tamaoki, T. et al. (Kyowa Hakko Kogyo Co., Ltd.;Fuji Photo Film Co., Ltd.) *Bisaryl cpds. and cancer remedies containing the same*. WO 0029375.

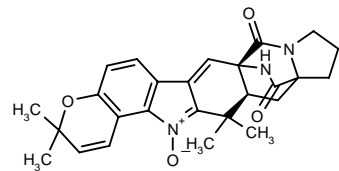
ANTIBIOTICS AND ALKALOIDS

AVRAINVILLAMIDE

289837

(+)-(7aR*,13aS*)-3,3,14,13-Tetramethyl-15-oxido-3,11,12,13,13a,14-hexahydro-8H,10H-7a,12a-(imino-methano)indolino[6,7-h]pyrano[3,2-a]carbazole-8,16-dione

CNC-358.445



C26 H27 N3 O4; Mol wt: 445.5163

ACTION – Cytotoxic compound isolated from the fermentation of the marine fungus *Aspergillus* sp. CNC358, shown to be active against a variety of tumor cell lines including human colon cancer HCT 116 cells (IC₅₀ = 2.0 μg/ml), malignant melanoma Malme-3M cells (IC₅₀ = 53 nM) and breast carcinoma BT-549 (IC₅₀ = 34 nM) and T-47D cells (IC₅₀ = 72 nM).

SOURCE – University of California, San Diego, La Jolla, CA (US).

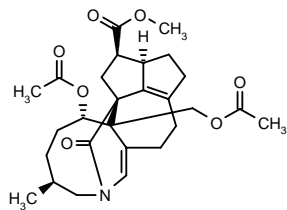
REFERENCES

1. Fenical, W. et al. (University of California, San Diego) *Avrainvillamide, a cytotoxic marine natural product, and derivs. thereof*. US 6066635.

DAPHNEZOMINE G

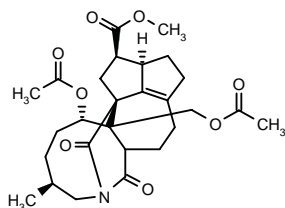
290586

(2R*,2aR*,10S*,13S*,13aS*,13bR*)-13-Acetoxy-13a-(acetoxymethyl)-10-methyl-14-oxo-8,13b-methano-2,2a,3,4,5,6,9,10,11,12,13,13a-dodecahydro-1H-cyclopent[1,8]azuleno[5,4-c]azonine-2-carboxylic acid methyl ester



C27 H35 N O7; Mol wt: 485.5735

ACTION – Antineoplastic alkaloid extracted from the stem of the plant *Daphniphyllum humile*, with cytotoxic activity against murine leukemia L1210 cells and human epidermoid carcinoma KB cells (IC_{50} = 5.3 and 7.3 μ g/ml, respectively). Another compound from this source is:



Daphnezomine F [290585]: C₂₇ H₃₅ N O₈

SOURCE – Hokkaido University, Sapporo (JP).

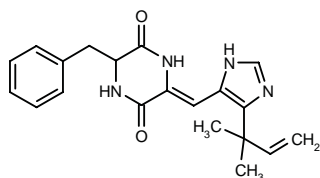
REFERENCES

1. Morita, H. et al. *Daphnezomines F and G: Novel alkaloids with 1-azabicyclo [5.2.2]undecane moiety from Daphniphyllum humile*. J Org Chem 2000, 65(11): 3558.

HALIMIDE

289996

3-Benzyl-6-[(Z)-4-(1,1-dimethyl-2-propenyl)-1H-imidazol-5-ylmethylidene]piperazine-2,5-dione



C₂₀ H₂₂ N₄ O₂; Mol wt: 350.4198

ACTION – Antineoplastic alkaloid isolated from the fermentation of the marine fungus *Aspergillus* sp. CNC139 (ATCC74434) that acts by inhibiting or reducing tubulin polymerization. *In vitro*, compound was shown to inhibit bovine brain tubulin polymerization in the presence of GTP by 55% at 20 μ M, and it exhibited cytotoxicity against human colon carcinoma HCT 116 and human ovarian carcinoma A2780 cells (IC_{50} = 1 and 0.8 μ M, respectively). It increased the life span of mice bearing murine P388 leukemia, giving a T/C x 100 value of 153% at a dose of 27 mg/kg/day i.p. x 5 days.

SOURCE – University of California, Oakland, Oakland, CA (US).

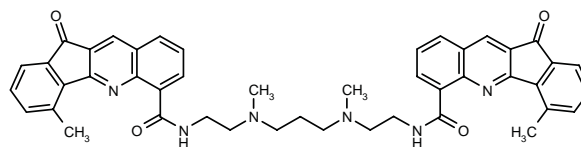
REFERENCES

1. Fenical, W. et al. (University of California, Oakland) *Halimide, a cytotoxic marine natural product, and derivs. thereof*. US 6069146.

DNA-INTERCALATING DRUGS

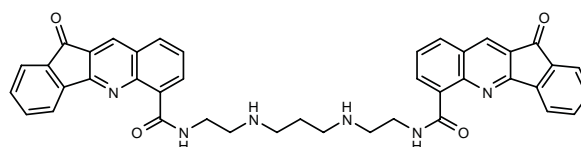
290417

N,N'-[1,3-Propanediylbis[(methylimino)-2,1-ethanediyl]]-bis[4-methyl-11-oxo-11H-indeno[1,2-b]quinoline-6-carboxamide]



C₄₅ H₄₂ N₆ O₄; Mol wt: 730.8648

ACTION – Antineoplastic agent from a new class of agents thought to act as inhibitors of topoisomerase I. The most lipophilic compound in the series, it exerted potent growth-inhibitory activity against wild-type murine leukemia P388, murine Lewis lung carcinoma and human Jurkat leukemia (IC_{50} = 7.9, 0.69 and 0.18 nM, respectively), as well as against amsacrine- and doxorubicin-resistant Jurkat leukemia (IC_{50} ratios = 0.4 and 0.6, respectively). In mice bearing s.c.-implanted colon 38 tumors, it induced a tumor growth delay of 7.5 days at a dose of 3.3 mg/kg/day i.p. every 4 days x 3, being at least as effective as irinotecan (growth delay of 7.0 days at 30 mg/kg/day). Another related compound is:



290418: C₄₁ H₃₄ N₆ O₄

SOURCES – University of Auckland, Auckland (NZ); La Trobe University, Bundoora, Victoria (AU).

REFERENCES

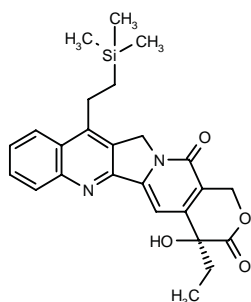
1. Deady, L.W. et al. (La Trobe University) *Topoisomerase inhibitors*. WO 9845272.
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BNP-1350

259669

7-[2-(Trimethylsilyl)ethyl]-20(*S*)-camptothecin4(*S*)-Ethyl-4-hydroxy-11-[2-(trimethylsilyl)ethyl]-1 *H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione

Karenitecin



C25 H28 N2 O4 Si; Mol wt: 448.5922

ACTION – Antineoplastic camptothecin derivative, an orally active, highly lipophilic topoisomerase I inhibitor with significant antitumor activity against human cancer cell lines including pediatric tumor cell lines such as medulloblastoma, neuroblastoma, osteosarcoma and rhabdomyosarcoma, as well as in animals bearing human tumors. In animal studies, compound given orally at doses of 0.5-2 mg/kg/day for 5-10 days demonstrated excellent antitumor activity, superior to that of topotecan, against common human solid tumors including prostate, colon, breast, lung and ovarian tumors and melanoma. It also possesses superior potency against a variety of common human cancers compared to existing camptothecin derivatives. Phase I clinical trials have shown antitumor activity, with dose-limiting toxicity consisting of reversible neutropenia and thrombocytopenia.

SOURCE – BioNumerik.

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2. Hausheer, F.H. et al. (BioNumerik Pharmaceuticals, Inc.) *Highly lipophilic camptothecin derivs.* WO 9807727.
3. Hausheer, F.H. et al. (BioNumerik Pharmaceuticals, Inc.) *Highly lipophilic camptothecin derivs.* WO 9835940.
4. Azrak, R.G. et al. *Altered phosphorylation of DNA damage checkpoint kinase CHK1 is associated with specific phases of cell cycle arrest by a novel topoisomerase I inhibitor BNP1350.* Proc Amer Assoc Cancer Res 2000, 41: Abst 185.
5. Boven, E. et al. *BNP1350 is a novel topoisomerase I inhibitor with high efficacy when given by oral route.* Proc Amer Assoc Cancer Res 1999, 40: Abst 750.
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14. van Hattum, A. et al. *Resistance against BNP1350 and other topoisomerase I inhibitors in variants of the human ovarian cancer cell line A2780.* Proc Amer Assoc Cancer Res 2000, 41: Abst 1896.

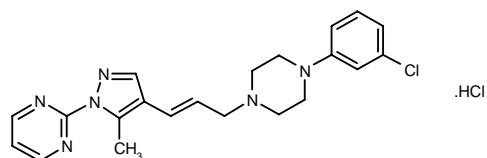
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ANTIMITOTIC DRUGS

DZ-3358

237135

1-(3-Chlorophenyl)-4-[3-[5-methyl-1-(2-pyrimidinyl)-pyrazol-4-yl]-1(*E*)-propenyl]piperazine hydrochloride

C21 H23 Cl N6 . HCl; Mol wt: 431.3686

M.p. 186-91 °C.

ACTION – Antineoplastic agent with antiproliferative activity against a panel of human cell lines (GI_{50} = 25-120 ng/ml). It induced arrest in the G2-M phase of the cell cycle in murine leukemia P388 cells and inhibited porcine tubulin polymerization (IC_{50} = 37.4 μ g/ml); immunofluorescence assays also indicated that compound inhibited microtubule formation in human gastric cancer NUGC-3 cells.

SOURCE – Daiichi Pharmaceutical.

REFERENCES

1. Ejima, A. et al. (Daiichi Pharmaceutical Co., Ltd.) *Pyrimidinylpyrazole deriv.* EP 0784055, JP 1997048776, US 5852019, WO 9610024.
2. Iwahana, M. et al. *Antiproliferative activity and mechanism of action of DZ-3358, a novel pyrimidinyl pyrazole derivative.* Anticancer Res 2000, 20(2A): 785.
3. Naito, H. et al. *Synthesis and antitumor activity of novel pyrimidinyl pyrazole derivatives.* Chem Pharm Bull 1999, 47(12): 1679.

HORMONAL AGENTS

S179D-PRL

290808

Human prolactin mutant in which the serine residue at position 179 has been replaced with aspartic acid

ACTION – Prolactin (PRL) receptor antagonist, a mutant of human PRL shown to inhibit the *in vitro* growth of androgen-sensitive human prostate cancer DU 145 cells and to reduce the formation of DU 145-derived tumors in nude mice. Potentially useful in the treatment of late-stage prostate cancer.

SOURCE – University of California, Riverside, Riverside, CA (US).

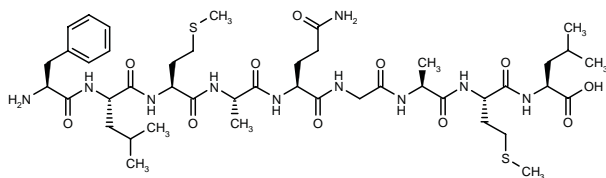
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2. Xu, X.L. et al. *Administration of the human PRL mutant, S179D, markedly reduces the incidence of tumors when DU145 human prostate cancer cells are grown in nude mice.* 82nd Annu Meet Endocr Soc (June 21-24, Toronto) 2000, Abst 722.
3. Yang, L. et al. *Administration of a prolactin receptor antagonist to pregnant rats resulted in increased fetal intrathymic apoptosis and no gamma δ T cell seeding of the epidermis.* 82nd Annu Meet Endocr Soc (June 21-24, Toronto) 2000, Abst 819.

CANCER IMMUNOTHERAPY

289709

L-Phenylalanyl-L-leucyl-L-methionyl-L-alanyl-L-glutaminyl-glycyl-L-alanyl-L-methionyl-L-leucine



C44 H72 N10 O11 S2; Mol wt: 981.2438

ACTION – Immunogenic polypeptide derived from a novel tumor-associated antigen designated CAMEL (CTL [Cytotoxic T-lymphocyte]-recognized Antigen on Melanoma), potentially useful in the immunotherapy of cancer. *In vitro*, compound was shown to concentration-dependently increase surface HLA-A2 expression on the transport-defective cell line 174CEM.T2.

SOURCES – Boehringer Ingelheim; Universiteit Leiden, Leiden (NL).

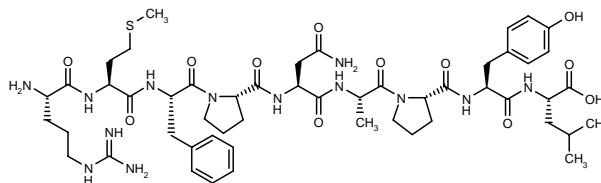
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1. Schrier, P.I. et al. (Boehringer Ingelheim GmbH; Universiteit Leiden) *CAMEL, an alternative translation product of the tumour antigen LAGE-1.* EP 1001022, WO 0023584.

WT-126-34

290054

L-Arginyl-L-methionyl-L-phenylalanyl-L-prolyl-L-asparaginy-L-alanyl-L-prolyl-L-tyrosyl-L-leucine



C52 H77 N13 O12 S; Mol wt: 1108.3250

ACTION – A representative compound from a series of novel peptides obtained based on the identification of peptide epitopes of two transcription factors aberrantly expressed in several cancers, namely WT-1 and gata-1, for use in the immunotherapy of cancer. Also disclosed is a method of producing activated cytotoxic T-lymphocytes (CTL) *in vitro*, as well as a method of killing cancer cells comprising the administration of said CTLs.

SOURCE – Imperial College Innovations.

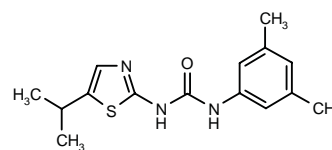
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INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

289797

N-(3,5-Dimethylphenyl)-N'-(5-isopropylthiazol-2-yl)urea



C15 H19 N3 O S; Mol wt: 289.4011

ACTION – Antineoplastic agent, a representative compound from a series of 2-ureidothiazole derivatives that acts by inhibiting cyclin-dependent kinase (cdk)/cyclin complexes, as demonstrated when tested in a cdk2/cyclin A inhibition assay ($K_i = 56 \mu\text{M}$).

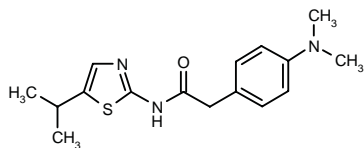
SOURCE – Pharmacia.

REFERENCES

1. Pevarello, P. et al. (Pharmacia & Upjohn SpA) *2-Ureido-thiazole derivs., process for their preparation, and their use as antitumor agents.* WO 0026203.

289798

2-[4-(Dimethylamino)phenyl]-N-(5-isopropylthiazol-2-yl)-acetamide



C16 H21 N3 O S; Mol wt: 303.4279

ACTION – Antineoplastic agent, a representative compound from a series of 2-aminothiazole derivatives that acts by inhibiting cyclin-dependent kinase (cdk)/cyclin complexes, as demonstrated when tested in a cdk2/cyclin A inhibition assay ($K_i = 0.1 \mu\text{M}$).

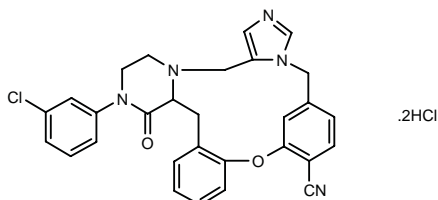
SOURCE – Pharmacia.

REFERENCES

1. Pevarello, P. et al. (Pharmacia & Upjohn SpA) *2-Amino-thiazole derivs., process for their preparation, and their use as antitumor agents*. WO 0026202.

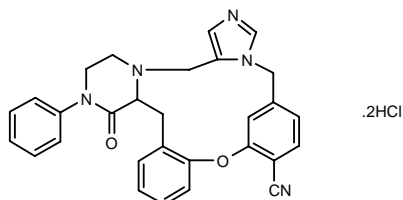
289841

(±)18-(3-Chlorophenyl)-17-oxo-16,16a,17,18,19,20-hexahydro-5H,22H-6,10-methenobenzo[b]imidazo-[4,3-h]pyrazino[2,1-e][1,6,9]oxadiazacyclopentadecine-9-carbonitrile dihydrochloride



C29 H24 Cl N5 O2 . 2HCl; Mol wt: 582.9164

ACTION – Inhibitor of protein farnesyltransferase ($\text{IC}_{50} = 10 \mu\text{M}$ or less) and the prenylation of the oncogene protein Ras, potentially useful for treating cancer, blindness related to retinal vascularization, hepatitis delta and related virus infections and polycystic kidney disease, and for preventing restenosis. Another specifically claimed peptidomimetic piperazine-containing macrocyclic compound is:



289842: C29 H25 N5 O2 . 2HCl

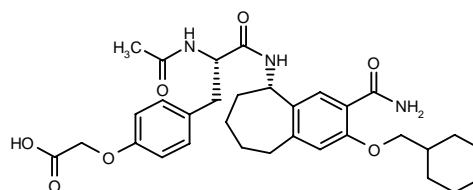
SOURCE – Merck & Co.

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1. Bergman, J.M. (Merck & Co., Inc.) *Inhibitors of prenyl-protein transferase*. WO 0025788.

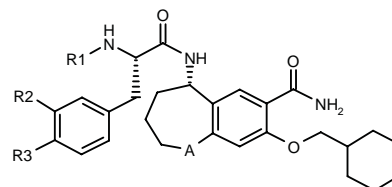
289968

2-[4-[2(S)-Acetamido-3-[3-carbamoyl-2-(cyclohexylmethoxy)-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5(S)-ylamino]-3-oxopropyl]phenoxy]acetic acid

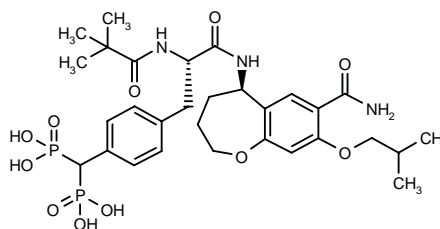


C32 H41 N3 O7; Mol wt: 579.6899

ACTION – Signal transduction inhibitor that especially inhibits intracellular signal transduction mediated by molecular interactions involving phosphotyrosine-containing proteins such as proteins containing one or more SH2 domains. It is therefore expected to be of use in the treatment of proliferative disorders, cancer, restenosis, osteoporosis, inflammation, allergies or cardiovascular diseases. Its use as an immunosuppressant is also specifically claimed. Other exemplified bicyclic compounds include the following:



Compound	R1	R2	R3	A	Formula
289969	Ac	CHO	CO2H	CH2	C ₃₂ H ₃₉ N ₃ O ₇
289971	H	PO3H2	PO3H2	O	C ₂₇ H ₃₇ N ₃ O ₁₀ P ₂
289972	Ac	OCH2CO2H	OCH2CO2H	CH2	C ₃₄ H ₄₃ N ₃ O ₁₀
289973	Ac	H	N(CH2CO2H) ₂	CH2	C ₃₄ H ₄₄ N ₄ O ₈



289970: C30 H43 N3 O11 P2

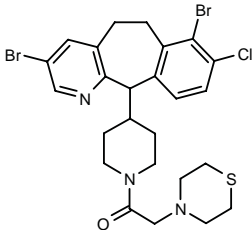
SOURCE – Ariad.

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1. Shakespeare, W.C. et al. (Ariad Pharmaceuticals Inc.) *Bicyclic signal transduction inhibitors, compsns. containing them & uses thereof*. WO 0027802.

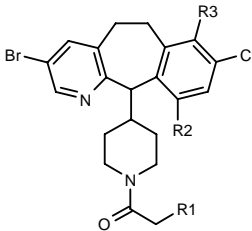
290221

1-[4-(3,7-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)piperidin-1-yl]-2-(4-thiomorpholinyl)-1-ethanone



C25 H28 Br2 Cl N3 O S; Mol wt: 613.8432

ACTION – Antineoplastic agent, a selective inhibitor of protein farnesyltransferase (IC₅₀ = 0.0089 μM against partially purified rat brain enzyme) and the farnesylation of the oncogene protein Ras. Other specifically claimed tricyclic compounds are:



Compound	R1	R2	R3	Formula
290226	1-oxido-4-thiomorpholinyl	H	Br	C ₂₅ H ₂₆ Br ₂ ClN ₃ O ₂ S
290228	1,3-dioxo-2-isoindolinyl	Cl	H	C ₂₉ H ₂₄ BrCl ₂ N ₃ O ₃

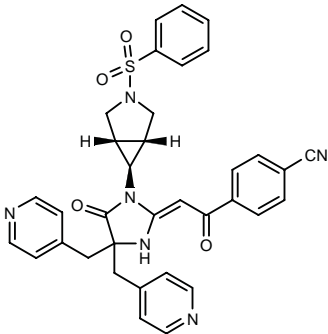
SOURCE – Schering-Plough.

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1. Njoroge, F.G. et al. (Schering Corp.) *Tricyclic cpds. useful as FPT inhibitors*. US 6071907.

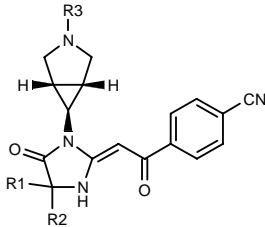
290459

(1α,5α,6α)-4-[2-[5-Oxo-1-[3-(phenylsulfonyl)-3-azabicyclo[3.1.0]hex-6-yl]-4,4-bis(4-pyridinylmethyl)imidazolidin-2-ylidene]acetyl]benzonitrile

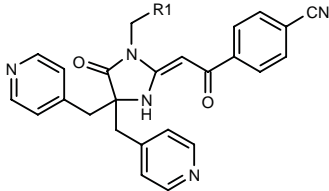


C35 H30 N6 O4 S; Mol wt: 630.7260

ACTION – Antineoplastic agent, a protein farnesyltransferase inhibitor. Other exemplified compounds from this series of 2-(2-oxo-ethylidene)imidazolin-4-one derivatives include the following:



Compound	R1	R2	R3	Formula
290461	4-Pyr-CH2	4-Pyr-CH2	4-Me-PhSO2	C ₃₆ H ₃₂ N ₆ O ₄ S
290463	4-Pyr-CH2	4-Pyr-CH2	4-(EtOCO)-1-Pip-SO2	C ₃₇ H ₃₈ N ₇ O ₆ S
290464	allyl	4-Pyr-CH2	t-BuOCO	C ₃₁ H ₃₃ N ₅ O ₄
290468	H	1-Me-5-imidazolyl	5-Br-2-thienyl-SO2	C ₂₈ H ₂₁ BrN ₆ O ₄ S ₂



Compound	R1	Formula
290466	1-(PhSO2)-4-Pip	C ₃₆ H ₃₄ N ₆ O ₄ S
290467	(1α,6α,7α)-3-(PhSO2)-3-azabicyclo[4.1.0]hept-7-yl	C ₃₇ H ₃₄ N ₆ O ₄ S
290470	8-(EtSO2)-8-azabicyclo[3.2.1]oct-3-yl	C ₃₄ H ₃₆ N ₆ O ₄ S
290471	4-Cl-Ph	C ₃₁ H ₂₄ ClN ₆ O ₂

SOURCE – Pfizer.

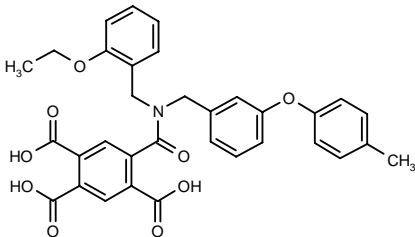
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A-176120

274450

5-[*N*-(2-Ethoxybenzyl)-*N*-[3-(4-methylphenoxy)benzyl]-carbamoyl]-1,2,4-benzenetricarboxylic acid



C33 H29 N O9; Mol wt: 583.5901

ACTION – Antineoplastic agent, a selective inhibitor of protein farnesyltransferase ($IC_{50} = 1.18$ nM) as opposed to the closely related enzymes geranylgeranyltransferase I, geranylgeranyltransferase II ($IC_{50} = 423$ and > 3000 nM, respectively) and squalene synthase ($IC_{50} > 10,000$ nM); kinetic studies demonstrated that compound competes with farnesylpyrophosphate ($K_i = 1.5$ nM), but not Ras, as a substrate for farnesyltransferase. In H-*ras*-transformed NIH3T3 cells and K-*ras*-mutated human colon carcinoma HCT116 cells, compound inhibited Ras processing ($ED_{50} = 1.6$ and 0.5 μ M, respectively). Antiangiogenic activity was demonstrated *in vitro* by its ability to inhibit Ras processing, cell proliferation and capillary structure formation in human umbilical vein endothelial cells, as well as by the decrease in the secretion of vascular endothelial growth factor (VEGF) from HCT116 cells. In addition, compound was able to inhibit the anchorage-dependent growth of K-*ras*-mutated HCT116 and pancreatic MiaPaCa-2 cells ($IC_{50} = 3$ and 0.87 μ M, respectively). *In vivo*, compound (at 50 or 100 mg/kg/day i.p. for 21 days) reduced tumor growth and prolonged life span in nude mice inoculated with H-*ras*- or K-*ras*-transformed NIH3T3 cells, and an additive effect was seen in combination with cyclophosphamide in nude mice inoculated with K-*ras*-transformed NIH3T3 cells.

SOURCE – Abbott.

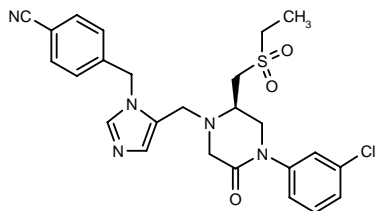
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2. Tahir, S.K. et al. *Biological properties of A-176120, a novel and potent farnesyl pyrophosphate analog*. Proc Amer Assoc Cancer Res 1999, 40: Abst 31.
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L-779575*

243314

4-[5-[4-(3-Chlorophenyl)-2(*R*)-(ethylsulfonylmethyl)-5-oxopiperazin-1-ylmethyl]-1*H*-imidazol-1-ylmethyl]-benzonitrile



C25 H26 Cl N5 O3 S; Mol wt: 512.0314

ACTION – Potent and selective protein farnesyltransferase inhibitor ($IC_{50} = 0.18$ and $> 100,000$ nM, respectively, against farnesyltransferase and geranylgeranyltransferase) able to inhibit the anchorage-independent growth of cultured H-*ras*-transformed RAT1 cells and breast cancer MCF-7 cells ($IC_{50} = 8$ and 5 nM, respectively). In nude mice bearing either H- or K-*ras*-dependent RAT1 cancer cells, compound at a dose of 14 mg/kg given by continuous s.c. infusion for 14 days reduced tumor cell growth by 100 and 60%, respectively.

SOURCE – Merck & Co.

REFERENCES

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*Identified compound **243314** (see **242862**) Drug Data Rep 1997, 019(02): 0171.

Mab 10C5

290853

Monoclonal antibody to human receptor for hyaluronic acid-mediated motility (RHAMM)

ACTION – Monoclonal antibody that inhibits the binding of hyaluronic acid to the human receptor for hyaluronic acid-mediated motility (RHAMM) in a microwell binding assay and interferes with *ras*-mediated signaling by blocking the platelet-derived growth factor (PDGF)-induced activation of p42/44 MAP kinase. Potentially useful for the treatment of proliferative diseases such as cancer, psoriasis, inflammatory bowel disease, rheumatoid arthritis and proliferative cardiovascular or ocular diseases. Other specifically claimed monoclonal antibodies are:

Mab 16E10 [290854]

Mab 3E6 [290855]

SOURCE – SmithKline Beecham.

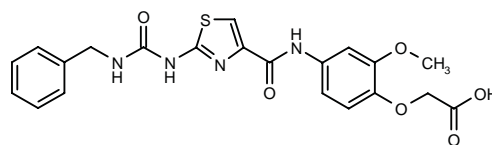
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ANGIOGENESIS INHIBITORS

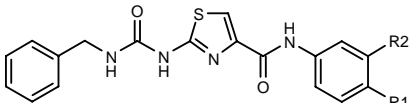
289528

2-[4-[2-(3-Benzylureido)thiazol-4-ylcarboxamido]-2-methoxyphenoxy]acetic acid



C21 H20 N4 O6 S; Mol wt: 456.4770

ACTION – An inhibitor of the binding of adhesive proteins such as fibrinogen, vitronectin, fibronectin, von Willebrand factor, thrombospondin and osteopontin to the vitronectin receptor ($\alpha_v\beta_3$) and related integrins such as $\alpha_v\beta_5$, $\alpha_v\beta_6$ and $\alpha_v\beta_8$ on the surface of various types of cells, thus influencing cell–cell and cell–matrix interactions. *In vitro*, compound exhibited an IC_{50} value of 0.2 nM for inhibition of the binding of fibrinogen to the human $\alpha_v\beta_3$ receptor. Potentially useful for the treatment or prevention of cancer, osteoporosis, Paget’s disease, diabetic retinopathy, macular degeneration, restenosis, psoriasis, arthritis, fibrosis, renal failure and bacterial, fungal and viral infections. Other specifically claimed compounds from this series of thiazole derivatives include the following:



Compound	R1	R2	Formula
289529	OCH2CO2Et	H	C ₂₂ H ₂₂ N ₄ O ₅ S
289530	OCH2CO2H	H	C ₂₀ H ₁₈ N ₄ O ₅ S
289531	OCH2CO2Et	OMe	C ₂₃ H ₂₄ N ₄ O ₆ S
289533	OCH2CO2Et	CO2CH2CO2Et	C ₂₇ H ₂₈ N ₄ O ₉ S
289534	OCH2CO2H	CO2H	C ₂₁ H ₁₈ N ₄ O ₇ S
289535	H	(E)-CH=CHCO2Et	C ₂₃ H ₂₂ N ₄ O ₄ S
289536	H	(E)-CH=CHCO2H	C ₂₁ H ₁₈ N ₄ O ₄ S

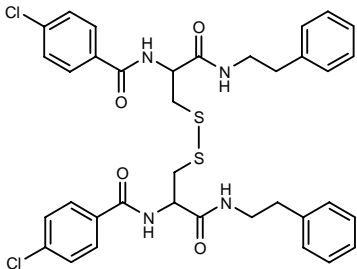
SOURCE – Roche.

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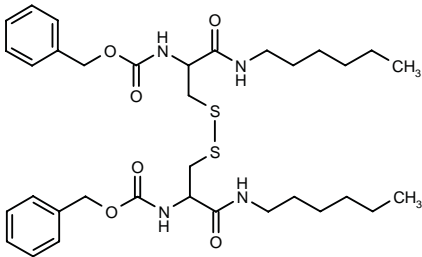
289947

N,N'-Bis(4-chlorobenzoyl)-DL-cystine bis(2-phenylethylamide)



C36 H36 Cl2 N4 O4 S2; Mol wt: 723.7424

ACTION – Nonpeptide cystine derivative for the treatment of matrix metalloproteinase (MMP)-related diseases; the compound is not active against MMPs ($K_i > 10 \mu\text{M}$), but is highly active *in vivo* in MMP-related diseases such as tumor growth and metastasis. Another exemplified compound is:



289948; C34 H50 N4 O6 S2

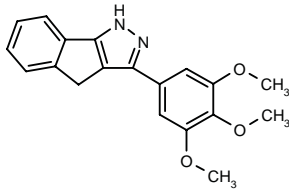
SOURCE – Roche Diagnostics.

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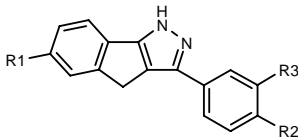
290142

3-(3,4,5-Trimethoxyphenyl)-1,4-dihydroindeno[1,2-*c*]pyrazole

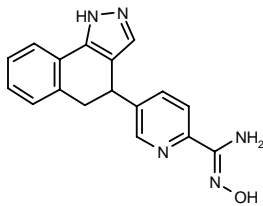


C19 H18 N2 O3; Mol wt: 322.3622

ACTION – An inhibitor of protein kinases, particularly tyrosine kinases involved in angiogenic and/or edematous processes such as KDR tyrosine kinase, with potential for the treatment of cancer, arthritis, atherosclerosis, psoriasis, hemangioma, myocardial angiogenesis, coronary and cerebral collateral vascularization, ischemic limb angiogenesis, corneal diseases, neovascular glaucoma, macular degeneration, wounds, ulcers, *Helicobacter*-related diseases, fractures, endometriosis and diabetic retinopathy, as well as burns, chronic lung disease, stroke, chronic and allergic inflammation, ovarian hyperstimulation syndrome and pulmonary and cerebral edema, among other disorders. Other specifically claimed compounds from this series of tricyclic pyrazole derivatives include the following:



Compound	R1	R2	R3	Formula
290143	H	CONHCH2CH2N(Et)2	H	C ₂₃ H ₂₆ N ₄ O
290145	H	CONHCH2CH2N(Me)2	H	C ₂₁ H ₂₂ N ₄ O
290146	H	perhydro-1,4-diazepin-1-yl- -CH2CH2NHCO	H	C ₂₄ H ₂₇ N ₅ O
290147	H	CONHCH(Me)Pr	H	C ₂₂ H ₂₃ N ₃ O
290148	H	NHCOCH(Me)Et	H	C ₂₁ H ₂₁ N ₃ O
290149	H	4-morpholinyl- -CH(Me)CH2NHCO	OH	C ₂₄ H ₂₆ N ₄ O ₃
290150	H	OH	4-Me-1-Piz- -(CH2)3NHCO	C ₂₅ H ₂₈ N ₅ O ₂
290151	NHAc	CO2Me	H	C ₂₀ H ₁₇ N ₃ O ₃



290144: C17 H15 N5 O

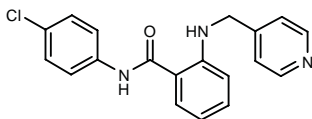
SOURCE – BASF.

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1. Doyle, K.J. et al. (BASF AG) *Tricyclic pyrazole derivs.* WO 0027822.

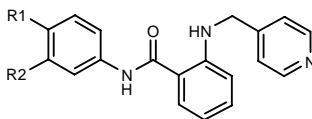
290199

N-(4-Chlorophenyl)-2-(4-pyridinylmethylamino)benzamide



C₁₉H₁₆ClN₃O; Mol wt: 337.8084

ACTION – An inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinase (IC₅₀ = 0.18 μM against Flt-1 VEGF receptor tyrosine kinase) and VEGF-dependent cell proliferation, with potential in the treatment of diseases associated with deregulated angiogenesis, particularly cancer, retinopathy and age-related macular degeneration, as well as inflammatory rheumatic or rheumatoid diseases and pain. Other exemplified compounds from this series of *N*-aryl(thio)anthranilic acid amide derivatives include the following:



Compound	R1	R2	Formula
290202	Me	H	C ₂₀ H ₁₉ N ₃ O
290204	Cl	CF ₃	C ₂₀ H ₁₅ ClF ₃ N ₃ O

SOURCE – Novartis.

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1. Altmann, K.-H. et al. (Novartis AG; Schering AG) *N*-Aryl(thio)anthranilic acid amide derivs., their preparation and their use as VEGF receptor tyrosine kinase inhibitors. WO 0027820.

MAb B9

291206

Monoclonal antibody to human α_vβ₃ and α_vβ₅ receptors

ACTION – Monoclonal antibody that specifically neutralizes α_vβ₃ and α_vβ₅ receptors and displays a serum half-life of about 60 h in animal models. This antibody is particularly useful as an antitumor, antiangiogenic, anti-inflammatory and antimetastatic agent.

SOURCE – SmithKline Beecham.

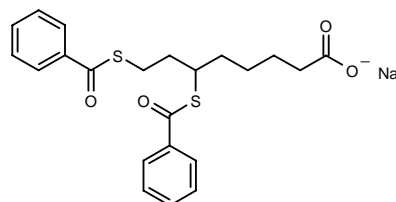
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1. Johnason, K.O. et al. (SmithKline Beecham Corp.) *Humanized monoclonal antibodies*. WO 0031248.

OTHER ONCOLYTIC DRUGS

289508

6,8-Bis(benzoylsulfanyl)octanoic acid sodium salt



C₂₂H₂₃NaO₄S₂; Mol wt: 438.5417

ACTION – Antineoplastic agent that selectively targets and kills tumor cells through inhibition of altered pyruvate dehydrogenase complex (PDC) activity. *In vitro*, compound was shown to kill a range of tumor cell lines, while having no effect on normal, noncancerous cells when tested at a concentration of 0.15 mM. Also reported to be useful for the treatment of other disease states involving altered energy metabolism including bacterial, fungal and protozoal infections.

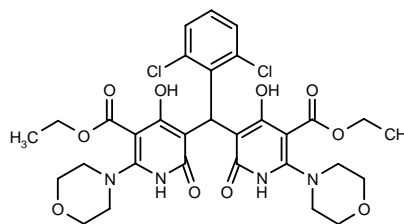
SOURCE – State University of New York, Albany, Albany, NY (US).

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290175

5,5'-[(2,6-Dichlorophenyl)methylene]bis[4-hydroxy-2-(4-morpholinyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid] diethyl ester



C₃₁H₃₄Cl₂N₄O₁₀; Mol wt: 693.5336

M.p. 260 °C.

ACTION – Antineoplastic agent with significant activity against a panel of 60 human tumor cell lines (GI₅₀ = 1.15-20.3 μM), as well as cytotoxic activity against 57 cell lines (LC₅₀ = 5.55-57.9 μM), selected for further evaluation in a hollow fiber assay *in vivo*.

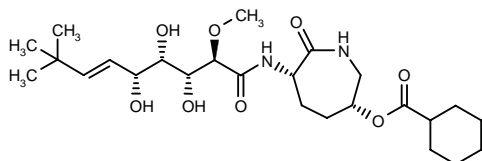
SOURCE – Università degli Studi di Cagliari, Cagliari (IT).

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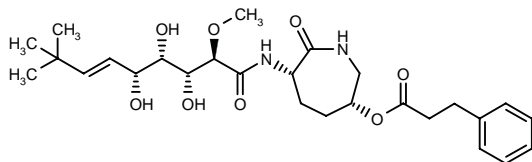
290302

Cyclohexanecarboxylic acid 7-oxo-6(*S*)-[(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-6-nonen-amido]perhydroazepin-3(*R*)-yl ester



C25 H42 N2 O8; Mol wt: 498.6128

ACTION – Antineoplastic agent with potent *in vitro* cytotoxicity against breast carcinoma MDA-MB-435 cells ($IC_{50} = 0.068 \pm 0.04 \mu M$ vs. $0.137 \pm 0.105 \mu M$ for doxorubicin). *In vivo*, it inhibited the growth of MDA-MB-435 xenografts implanted s.c. in nude mice, giving T/C x 100 values of 61, 24 and –6, respectively, at 10, 33 and 100 $\mu mol/kg$ i.v. 3 times per week x 3 weeks, compared to a T/C x 100 value of 42 for doxorubicin at 2 mg/kg i.v. Another specifically claimed compound from this series of substituted caprolactams is:



290304: C27 H40 N2 O8

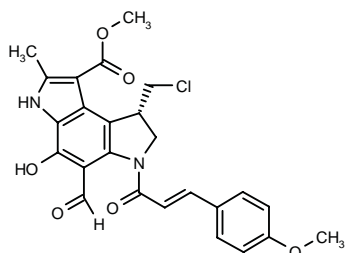
SOURCE – Novartis.

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290440

8(*S*)-(Chloromethyl)-5-formyl-4-hydroxy-2-methyl-6-[3-(4-methoxyphenyl)-2(*E*)-propenoyl]-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b'*]dipyrrole-1-carboxylic acid methyl ester



C25 H23 Cl N2 O6; Mol wt: 482.9177

ACTION – Antineoplastic agent, a duocarmycin derivative with relatively weak cytotoxic activity against HeLa S3 cells ($IC_{50} = 190$ and 29 nM, respectively, after 1- and 72-h incubation) but highly potent *in vivo* activity in mice bearing murine sarcoma 180 (T/C = 0.14 at a dose of 16 mg/kg i.v.) and low peripheral blood toxicity.

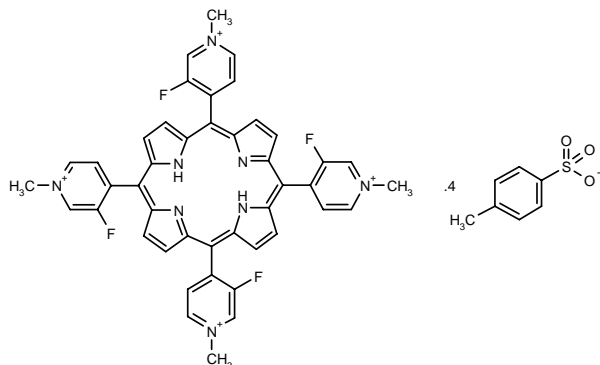
SOURCE – Kyowa Hakko.

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291271

5,10,15,20-Tetrakis(3-fluoro-1-methylpyridinium-4-yl)porphyrin tetra(4-methylbenzenesulfonate)



C44 H34 F4 N8 . 4 C7 H7 O3 S; Mol wt: 1435.5820

ACTION – Potent and reversible acetylcholinesterase inhibitor ($K_i = 3.06 \mu M$), a water-soluble porphyrin with a broad spectrum of anticancer activity *in vitro* and good anticancer activity *ex vivo* against leukemia HL-60 and melanoma B16BL6 cells. In addition, compound exhibited potent antiangiogenic activity *in vivo* in the chick chorioallantoic membrane (CAM) assay, as well as antimutational activity in the Ames test *in vitro*. Potentially useful as an anticancer agent and for the treatment of Alzheimer's disease.

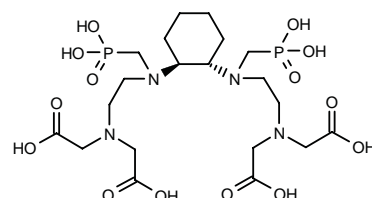
SOURCES – Seoul National University, Seoul (KR); Seoul Women's University, Seoul (KR); Wonkwang University, Cheonbuk (KR).

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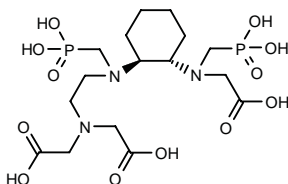
AL-245**289505**

N,N'-(*trans*-Cyclohexane-1,2-diyl)bis(phosphonomethyl-imino)bis(aminodiacetic acid)



C20 H38 N4 O14 P2; Mol wt: 620.4822

ACTION – Semirigid chelating agent able to form complexes with radioactive elements, particularly α -, β - or γ -emitting radiometals and preferably from the actinide or lanthanide groups. The complexes with α - and β -emitting radiometals are useful for the therapy of cancer and those emitting γ radiation may be used in diagnostic procedures such as radioimmunoscinigraphy. AL-245 has shown very good complexation properties for ^{153}Sm , with no loss of radiometal from the complex at 24, 48, 72 and 96 h at 37 °C in human serum. Another related compound is:



AL-247 [289506]: C16 H31 N3 O12 P2

SOURCE – INSERM, Paris Cedex (FR).

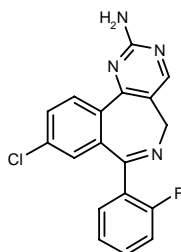
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BBL22

290670

9-Chloro-7-(2-fluorophenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-amine



C18 H12 Cl F N4; Mol wt: 338.7718

ACTION – Selective ligand for peripheral benzodiazepine binding sites proven to induce arrest in the G2/M phase of the cell cycle in human tumor cell lines of both hematopoietic and epithelial cellular origin; after G2/M arrest, several tumor types including prostate and certain breast cancer cell lines exhibited significant apoptosis. Compound did not affect the growth and survival of nonmalignant breast and prostate epithelial lines. *In vivo*, in nude mice bearing androgen-independent prostate PC3 tumors, doses of 50 or 250 mg/kg/day i.p. for 4 days significantly inhibited tumor growth without significant toxicity.

SOURCES – Bessor and Bessor Laboratories; University of Miami, Miami, FL (US).

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GEMTUZUMAB OZOGAMICIN

198455

Immunoglobulin G4 (anti-[human CD33 (antigen)] [human-mouse monoclonal hP67.6 γ_4 -chain]), disulfide with human-mouse monoclonal hP67.6 κ -chain, dimer conjugated to [(1R,4Z,8S,13E)-[8-[[2-O-[4-(acetyloethyl-amino)-2,4-dideoxy-3-O-methyl- α -L-threo-pentopyranosyl]-4,6-dideoxy-4-[[[2,6-dideoxy-4-S-[4-[(6-deoxy-3-O-methyl- α -L-mannopyranosyl)oxy]-3-iodo-5,6-dimethoxy-2-methylbenzoyl]-4-thio- β -D-ribo-hexopyranosyl]oxy]amino]- β -D-glucopyranosyl]oxy]-13-[2-[[3-[[1-[4-(4-amino-4-oxobutoxy)phenyl]ethylidene]hydrazino]-1,1-dimethyl-3-oxopropyl]dithio]ethylidene]-1-hydroxy-11-oxobicyclo-[7.3.1]trideca-4,9-diene-2,6-diyn-10-yl]carbamic acid methyl ester

CDP-771

CMA-676

Gemtuzumab zogamicin⁺

hP67.6-calicheamicin

WAY-CMA-676

ACTION – Recombinant humanized antibody that binds specifically to the CD33 antigen on the surface of leukemic myeloblasts and immature normal cells of myelomonocytic lineage, but not normal hematopoietic stem cells, conjugated with the cytotoxic antitumor antibiotic calicheamicin. Upon internalization of the complex, the calicheamicin derivative is released inside the lysosomes of the myeloid cell and binds to DNA in the minor groove, resulting in DNA double-strand breaks and cell death.

INDICATION – Treatment of patients with CD33-positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy.

PRESENTATION – Vials (20 ml) of lyophilized powder, 5 mg.

PROPRIETARY NAME – Mylotarg (US).

SOURCES – Codeveloped by Celltech Group and Wyeth-Ayerst.

REFERENCES

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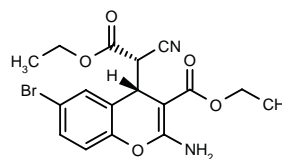
MONOGRAPH – Rabasseda, X. et al. *Gemtuzumab Ozogamicin*. Drugs Fut 2000, 25(7): 0686.

*Drug Data Rep 2000, 022(03): 0281.

HA-14-1

290669

2-Amino-6-bromo-4(S)-[1(S)-cyano-2-ethoxy-2-oxoethyl]-4H-1-benzopyran-3-carboxylic acid ethyl ester



C17 H17 Br N2 O5; Mol wt: 409.2343

ACTION – Apoptotic agent, a nonpeptide ligand for the Bcl-2 protein surface pocket ($IC_{50} = 9 \mu M$) proven to induce apoptosis in human acute myeloid leukemia HL-60 cells overexpressing Bcl-2 protein (90% loss of viability at $50 \mu M$). The induction of apoptosis was associated with activation of caspase 9, followed by caspase 3 and Apaf-1, and is independent of the Fas/TNF pathway.

SOURCE – Thomas Jefferson University, Philadelphia, PA (US).

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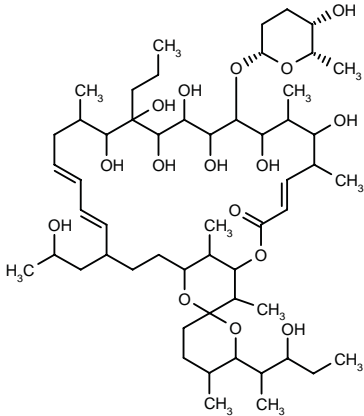
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IB-96212

289753

(4*E*,18*E*,20*E*)-7,9,11,12,13,14,15-Heptahydroxy-6'-(2-hydroxy-1-methylbutyl)-22-(2-hydroxypropyl)-5',6,8,16,28,29-hexamethyl-14-propyl-10-(2,3,6-trideoxy-β-L-galactopyranosyloxy)-3',4',5',6'-tetrahydrospiro[2,26-dioxabicyclo[23.3.1]nonacosa-4,18,20-triene-27,2'-[2*H*]pyran]-3-one



C54 H94 O16; Mol wt: 999.3206

Pale white crystalline powder, m.p. 165-6 °C.

ACTION – Cytotoxic macrolide isolated from the marine sponge *Micromonospora* sp. strain L-25-ES25-008, with very strong activity against murine leukemia P388 cells (IC₅₀ = 0.1 mg/ml) and significant activity against human colon cancer HT-29 cells, human lung carcinoma A549 cells and human melanoma MEL-28 cells (IC₅₀ = 1 µg/ml). Compound exhibited antimicrobial activity only against *Micrococcus luteus* (MIC = 0.4 µg/ml).

SOURCES – Instituto Biomar; PharmaMar.

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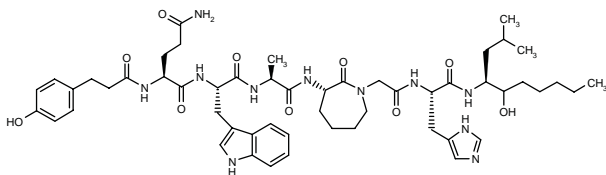
2. Cañedo, L.M. et al. *IB-96212, a novel cytotoxic macrolide produced by a marine Micromonospora. II. Physico-chemical properties and structure determination*. J Antibiot 2000, 53(5): 479.

3. Fernández-Chimeno, R.I. et al. *IB-96212, a novel cytotoxic macrolide produced by a marine Micromonospora. I. Taxonomy, fermentation, isolation and biological activities*. J Antibiot 2000, 53(5): 474.

JMV-1802

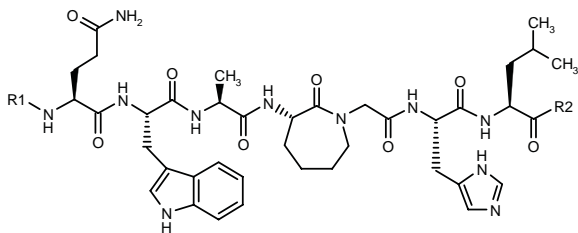
290360

*N*²-[2-[3(*S*)-[*N*-[3-(4-Hydroxyphenyl)propionyl]-L-glutaminyl-L-tryptophyl-L-alanyl-amino]-2-oxoperhydroazepin-1-yl]-acetyl]-*N*¹-[1(*S*)-isobutyl-2-hydroxyheptyl]-L-histidinamide



C53 H75 N11 O10; Mol wt: 1026.2430

ACTION – Bombesin analogue that binds gastrin-releasing peptide (GRP)/bombesin receptors on rat pancreatic acini and in Swiss 3T3 cells (K_i = 3.8 and 0.8 nM, respectively). It exhibited antagonist properties versus bombesin, as demonstrated by its ability to antagonize amylase secretion from rat pancreatic acini (K_i = 3.3 nM) and the bombesin-stimulated proliferation of Swiss 3T3 cells (K_i = 0.5 nM); no agonist activity on rat pancreatic acini or in Swiss 3T3 cells was seen at up to 1 µM. Potentially useful for inhibiting the physiological response to GRP in human diseases including small cell lung carcinoma. Other constrained bombesin analogues include the following:



Compound	R1	R2	Formula
JMV-1535 [290358]	H-L-Phe-	-L-Leu-NH2	C ₅₄ H ₇₆ N ₁₄ O ₁₀
JMV-1799 [290359]	4-OH-PhCH2CH2CO	OMe	C ₄₈ H ₆₅ N ₁₁ O ₁₁

SOURCES – CNRS; Université Montpellier I, Montpellier, (FR); Université Montpellier II, Montpellier (FR).

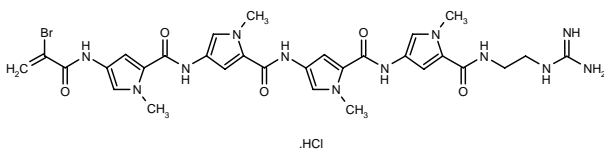
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1. Cristau, M. et al. *Synthesis and biological evaluation of bombesin constrained analogues*. J Med Chem 2000, 43(12): 2356.

PNU-166196*

262512

2-[4-[4-[4-(2-Bromo-2-propenamido)-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]ethylguanidine hydrochloride



C30 H35 Br N12 O5 . HCl; Mol wt: 760.0504

ACTION – Antineoplastic agent, a distamycin A derivative that exhibits potent cytotoxic activity against human and murine tumor cell lines *in vitro*, with a mean IC₅₀ value of about 29 ng/ml. Compound showed potent antitumor activity and a high therapeutic index in experimental tumor models; at the maximum tolerated dose (MTD) of 0.78 mg/kg i.v. x 3, it was active against human ovarian carcinoma A2780 (99% tumor inhibition) and H207 (100% tumor inhibition), renal carcinoma Caki-2 (84% tumor inhibition), prostatic carcinoma DU 145 (77% tumor inhibition), mammary carcinoma MX-1 (76% tumor inhibition) and lung carcinoma N592 (72% tumor inhibition) xenografts; less activity was seen against colon carcinoma HCT 116 (> 60% tumor inhibition) and gastric carcinoma GTL16. Furthermore, it was significantly more active than tallimustine in inducing apoptosis in human ovarian carcinoma A2780 cells and is reportedly able to circumvent resistance to alkylating agents and topoisomerase I inhibitors both *in vitro* and *in vivo*. Unlike tallimustine, compound was seen to bind to but not alkylate DNA minor groove AT-rich sequences. Currently undergoing phase I clinical trials.

SOURCE – Pharmacia.

REFERENCES

1. Cozzi, P. et al. (Pharmacia & Upjohn AB) *Acryloyl substd. distamycin derivs., process for preparing them, and their use as antitumor and antiviral agents*. WO 9804524.
2. Ciomei, M. et al. *Induction of apoptosis with a new distamycin derivative*. Proc Amer Assoc Cancer Res 1999, 40: Abst 1490.
3. Cozzi, P. et al. *Cytotoxic α -bromoacrylic derivatives of distamycin analogues modified at the amidino moiety*. Bioorg Med Chem Lett 2000, 10(11): 1273.
4. Geroni, C. et al. *Antitumor activity of PNU-166196, a novel DNA minor groove binder selected for clinical development*. Proc Amer Assoc Cancer Res 2000, 41: Abst 1689.
5. Geroni, C. et al. *Antitumor activity of PNU-166196, a novel DNA minor groove binder selected for clinical development*. Proc Amer Assoc Cancer Res 2000, 41: Abst 2708.
6. Giusti, A.M. et al. *In vivo induction of apoptosis with PNU-166196 in human ovarian carcinoma xenografts*. Proc Amer Assoc Cancer Res 2000, 41: Abst 5240.

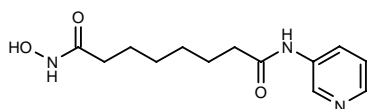
*Identified compound **262512** (see **261569**) Drug Data Rep 1998, 020(05): 0450.

PYROXAMIDE

287630

N'-Hydroxy-*N*-(3-pyridyl)octane-1,8-diamide

NSC-696085



C13 H19 N3 O3; Mol wt: 265.3111

ACTION – Hydroxamic acid-based hybrid polar compound proven to induce differentiation of transformed cells and to inhibit histone deacetylase. Preclinical toxicological experiments showed that it induced myelosuppression at the maximum tolerated dose in both rats and dogs, and gastrointestinal toxicity (emesis, diarrhea) in dogs. Compound showed an oral bioavailability of 25% in mice, and pharmacokinetic studies in dogs showed a similar distribution and metabolism of compound after i.v. bolus doses or 24-h continuous infusion. Compound is entering phase I trials.

SOURCE – National Cancer Institute, Bethesda, MD (US).

REFERENCES

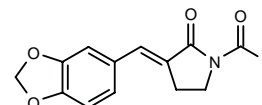
1. Eiseman, J.L. et al. *Murine plasma pharmacokinetics of the hybrid polar compound, pyroxamide (NSC696085)*. Proc Amer Assoc Cancer Res 2000, 41: Abst 4903.
2. Noker, P.E. et al. *Pharmacokinetics of pyroxamide (NSC-696085), a hybrid polar compound, in beagle dogs*. Proc Amer Assoc Cancer Res 2000, 41: Abst 4904.
3. Noker, P.E. et al. *Preclinical toxicity of pyroxamide (NSC-696085) in dogs and rats*. Proc Amer Assoc Cancer Res 2000, 41: Abst 4902.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

KNK-437*

272339

3-[(*E*)-1,3-Benzodioxol-5-ylmethylene]-2-oxopyrrolidine-1-carbaldehyde



C13 H11 N O4; Mol wt: 245.2329

ACTION – An inhibitor of the acquisition of thermotolerance that acts via inhibition of the induction of heat shock proteins (HSPs). In human colon carcinoma COLO 320DM cells with acquired thermotolerance induced by fractionated heat treatment, compound at a concentration of 100 μ M almost completely inhibited the development of thermotolerance when added prior to the first heat treatment until after the second treatment, and was much more effective than quercetin. No toxic effects to the cells were seen even at concentrations of up to 200 μ M and it did not increase thermosensitivity in nontolerant cells. In addition, at the above concentration it was shown to inhibit the induction of HSPs including HSP105, HSP70 and HSP40 in COLO 320DM cells, while having no effect on other proteins. Other experiments demonstrated that compound inhibits HSP70 synthesis at the mRNA level. Potentially useful as a sensitizer for cancer hyperthermic therapy.

SOURCE – Kaneka.

REFERENCES

1. Yokota, S. et al. (Kaneka Corp.) *Heat shock factor activity inhibitors*. EP 0995745, WO 9900382.
2. Yokota, S. et al. *Benzylidene lactam compound, KNK437, a novel inhibitor of acquisition of thermotolerance and heat shock protein induction in human colon carcinoma cells*. Cancer Res 2000, 60(11): 2942.

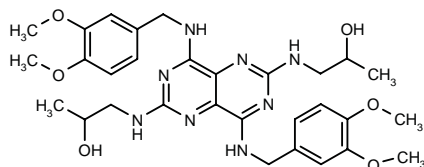
*Identified compound **272339** Drug Data Rep 1999, 021(03): 0207.

NU-3108

287191

1-[4,8-Bis(3,4-dimethoxybenzylamino)-6-(2-hydroxypropylamino)pyrimido[5,4-*d*]pyrimidin-2-ylamino]-2-propanol

1,1'-[[4,8-Bis(3,4-dimethoxybenzylimino)pyrimido[5,4-*d*]pyrimidine-2,6-diyl]diimino]bis(2-propanol)



C30 H40 N8 O6; Mol wt: 608.6960

ACTION – Nucleoside transport inhibitor, a dipyridamole analogue whose activity was demonstrated by potent inhibition of thymidine uptake into murine leukemia L1210 cells ($IC_{50} = 310$ nM). Compound was able to potentiate the antitumor activity of antifolate antimetabolites such as LY-231514 and LY-309887. In particular, it potentiated the growth-inhibitory activity of LY-231514 in human non-small cell lung cancer A549 and COR L23 cells by inhibiting thymidine and hypoxanthine rescue both in the presence and absence of α_1 -acid glycoprotein. Good stability in human plasma was seen, with only 20% degradation over 48 h. Pharmacokinetic studies in mice showed that the compound (at doses of 2 and 20 mg/kg i.p.) was rapidly absorbed ($t_{max} = 10$ min), and plasma levels following a dose of 2 mg/kg i.p. remained above the effective concentration for 15 min. Dose-dependent hypothermia was observed in mice at 5-20 mg/kg, suggesting a pharmacological effect that may be attributable to vasodilatation via increased plasma adenosine levels. Studies with compound are currently in progress in tumor xenograft models.

SOURCE – University of Newcastle upon Tyne, Newcastle upon Tyne (GB).

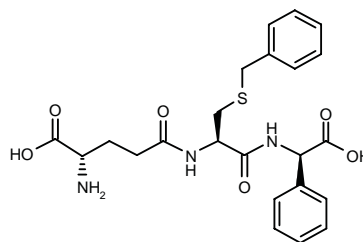
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1. Barlow, H.C. et al. *Resistance-modifying agents. Part 7: 2,6-Disubstituted-4,8-dibenzylaminopyrimido[5,4-*d*]pyrimidines that inhibit nucleoside transport in the presence of α_1 -acid glycoprotein.* Bioorg Med Chem Lett 2000, 10(6): 585.
2. Curtin, N.J. et al. *Development of nucleoside transport inhibitors to potentiate antimetabolite anticancer drugs.* Drug Dev Res 2000, 50(1): Abst W01-04.
3. Thomas, H.D. et al. *In vitro activity and in vivo pharmacology of a novel nucleoside transport inhibitor NU3108.* Proc Amer Assoc Cancer Res 2000, 41: Abst 3130.

TER-117

289992

L-Glutamyl-S-(benzyl)-L-cysteinyl-D-phenylglycine



C23 H27 N3 O6 S; Mol wt: 473.5473

ACTION – Glutathione analogue, a selective inhibitor of human glutathione *S*-transferase P1-1 (GST P1-1; $K_i = 0.12$ - 0.14 μ M) that is also able to inhibit human glyoxalase I ($K_i = 0.56$ μ M). Compound is an effective inhibitor of multidrug resistance-associated protein (MRP1) and was found to reversibly inhibit ATP-dependent 2,4-dinitrophenyl-2-glutathione transport in MRP1-containing NIH3T3 membrane vesicles with a K_i of 752 μ M, suggesting that it is a substrate for MRP1. Potentially useful for improving the efficacy of chemotherapy.

SOURCE – Telik.

REFERENCES

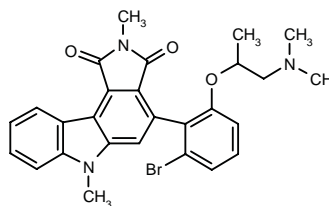
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3. Lyttle, M.H. et al. *Isozyme-specific glutathione-S-transferase: Design and synthesis.* J Med Chem 1994, 37(1): 189.
4. Shen, H. et al. *Glutathione conjugate interactions with DNA-dependent protein kinase.* J Pharmacol Exp Ther 1999, 290(3): 1101.
5. Wang, K. et al. *Glutathione S-transferase in wild-type and doxorubicin-resistant MCF-7 human breast cancer cell lines.* Xenobiotica 1999, 29(2): 155.

CHEMOPROTECTIVE AGENTS

KF-41399*

264987

4-[2-Bromo-6-[2-(dimethylamino)-1-methylethoxy]phenyl]-2,6-dimethyl-1,2,3,6-tetrahydropyrrolo[3,4-*c*]carbazole-1,3-dione



C27 H26 Br N3 O3; Mol wt: 520.4244

ACTION – Chemoprotective agent, a carbazole derivative shown to improve the severe thrombocytopenia induced by nimustine in mice when given before the chemotherapeutic agent. In addition, compound improved other toxic effects caused by the maximum tolerated doses of nimustine such as the decreases in body weight, spleen weight and colony-forming activity of bone marrow mononuclear cells. In contrast, it did not affect the antitumor activity of nimustine in mice bearing sarcoma 180 or human lung cancer LC-6 tumors, although it slightly reduced the antitumor activity of nimustine against human lung cancer Lu-65 xenografts. Studies in normal mice showed that compound (25 mg/kg p.o.) induces G0/G1 cell cycle arrest in bone marrow progenitor cells, which was associated with upregulation of Bcl-2 protein and downregulation of cyclin E and cyclin A proteins. Potentially useful for the treatment of myelosuppression caused by chemotherapy.

SOURCE – Kyowa Hakko.

REFERENCES

1. Ino, Y. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Pyrrolocarbazole derivs.* WO 9809967.
2. Kanai, F. et al. *Synthesis and structure-activity relationships of pyrrolocarbazole derivatives possessing the oral thrombopoietic activity.* 27th Natl Med Chem Symp (June 13-17, Kansas City) 2000, Abst A-03.
3. Shiotsu, Y. et al. *Chemoprotective effects of KF41399, a derivative of carbazole compounds, on nimustine-induced thrombocytopenia.* Blood 2000, 95(12): 3771.
4. Shiotsu, Y. et al. *Oral administration effect of KF41399, a derivative of carbazole compounds, on ACNU induced thrombocytopenia (2).* Int J Hematol 1999, 69(Suppl. 1): Abst 532.
5. Yamashita, K. et al. *Oral administration effect of KF41399, a derivative of carbazole compounds, on ACNU induced thrombocytopenia (1).* Int J Hematol 1999, 69(Suppl. 1): Abst 531.
6. *New carbazole from Kyowa Hakko effective against chemotherapy-induced thrombocytopenia.* DailyDrugNews.com (Daily Essentials) 1999, June 4.

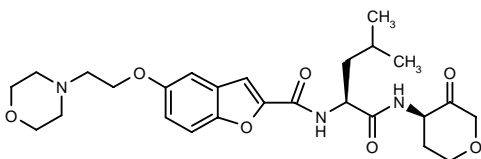
*Identified compound **264987** (see **263805**) Drug Data Rep 1998, 020(06): 0554.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

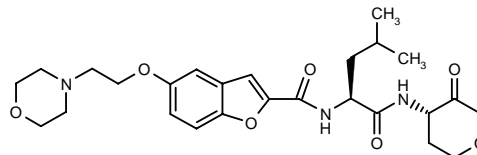
290232

*N*²-[5-[2-(4-Morpholinyl)ethoxy]benzofuran-2-ylcarbonyl]-*N*¹-[3-oxotetrahydropyran-4(*R*)-yl]-L-leucinamide



C26 H35 N3 O7; Mol wt: 501.5765

ACTION – An inhibitor of cysteine proteases of the papain superfamily, particularly cathepsin K, potentially useful for inhibiting bone loss, as well as for the treatment of osteoporosis, gingival or periodontal disease and diseases characterized by excessive cartilage or matrix degradation such as osteoarthritis and rheumatoid arthritis. Another specifically claimed compound from this series of morpholino-ethoxybenzofuran derivatives is:



290233: C26 H35 N3 O7

SOURCE – SmithKline Beecham.

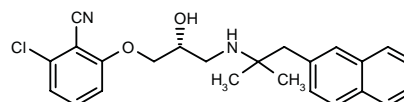
REFERENCES

1. Gribble, A.D. and Witherington, J. (SmithKline Beecham plc) *Morpholino-ethoxybenzofuran protease inhibitors.* WO 0029408.

NPS-2143

270642

2-Chloro-6-[3-[1,1-dimethyl-2-(2-naphthalenyl)ethyl-amino]-2(*R*)-hydroxypropoxy]benzonitrile



C24 H25 Cl N2 O2; Mol wt: 408.9265

ACTION – Selective antagonist of the parathyroid cell Ca²⁺ receptor proven to inhibit extracellular Ca²⁺-induced increases in cytoplasmic Ca²⁺ levels in human parathyroid Ca²⁺ receptor-expressing HEK293 cells (IC₅₀ = 43 nM), and to stimulate parathyroid hormone (PTH) secretion in bovine parathyroid cells (EC₅₀ = 39 nM). In osteopenic ovariectomized rats, compound given orally at the dose of 100 mg/kg/day for 8 weeks induced moderate but sustained increases in plasma PTH levels and marked increases in bone turnover (increase in both bone formation and resorption), with no net bone gain or loss. Combination of oral compound and 17β-estradiol by s.c. infusion also produced an increase in bone turnover, but the antiresorptive effect of estrogen led to a decrease in the extent of bone resorption associated with elevated PTH levels, resulting in a net increase in bone mass compared to ovariectomized controls or animals treated with either drug alone. Potentially useful for the treatment of osteoporosis.

SOURCES – NPS Pharmaceuticals; SmithKline Beecham.

REFERENCES

1. Gowen, M. et al. *Antagonizing the parathyroid calcium receptor stimulates parathyroid hormone secretion and bone formation in osteopenic rats.* J Clin Invest 2000, 105(11): 1595.
2. Nemeth, E.F. et al. *Stimulation of parathyroid hormone secretion by a small molecule antagonist of the calcium receptor.* 2nd Jt Meet Am Soc Bone Miner Res Int Bone Miner Soc (Dec 1-6, San Francisco) 1998, Abst 1030.

ACTION – Chemoprotective agent, a carbazole derivative shown to improve the severe thrombocytopenia induced by nimustine in mice when given before the chemotherapeutic agent. In addition, compound improved other toxic effects caused by the maximum tolerated doses of nimustine such as the decreases in body weight, spleen weight and colony-forming activity of bone marrow mononuclear cells. In contrast, it did not affect the antitumor activity of nimustine in mice bearing sarcoma 180 or human lung cancer LC-6 tumors, although it slightly reduced the antitumor activity of nimustine against human lung cancer Lu-65 xenografts. Studies in normal mice showed that compound (25 mg/kg p.o.) induces G0/G1 cell cycle arrest in bone marrow progenitor cells, which was associated with upregulation of Bcl-2 protein and downregulation of cyclin E and cyclin A proteins. Potentially useful for the treatment of myelosuppression caused by chemotherapy.

SOURCE – Kyowa Hakko.

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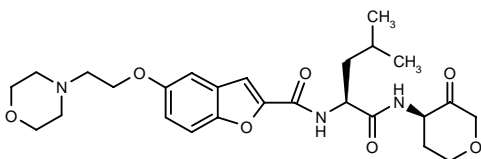
*Identified compound **264987** (see **263805**) Drug Data Rep 1998, 020(06): 0554.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

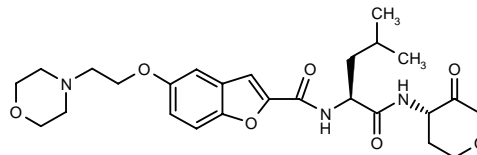
290232

*N*²-[5-[2-(4-Morpholinyl)ethoxy]benzofuran-2-ylcarbonyl]-*N*¹-[3-oxotetrahydropyran-4(*R*)-yl]-L-leucinamide



C26 H35 N3 O7; Mol wt: 501.5765

ACTION – An inhibitor of cysteine proteases of the papain superfamily, particularly cathepsin K, potentially useful for inhibiting bone loss, as well as for the treatment of osteoporosis, gingival or periodontal disease and diseases characterized by excessive cartilage or matrix degradation such as osteoarthritis and rheumatoid arthritis. Another specifically claimed compound from this series of morpholino-ethoxybenzofuran derivatives is:



290233: C26 H35 N3 O7

SOURCE – SmithKline Beecham.

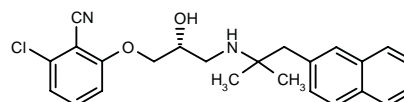
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NPS-2143

270642

2-Chloro-6-[3-[1,1-dimethyl-2-(2-naphthalenyl)ethyl-amino]-2(*R*)-hydroxypropoxy]benzonitrile



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ACTION – Selective antagonist of the parathyroid cell Ca²⁺ receptor proven to inhibit extracellular Ca²⁺-induced increases in cytoplasmic Ca²⁺ levels in human parathyroid Ca²⁺ receptor-expressing HEK293 cells (IC₅₀ = 43 nM), and to stimulate parathyroid hormone (PTH) secretion in bovine parathyroid cells (EC₅₀ = 39 nM). In osteopenic ovariectomized rats, compound given orally at the dose of 100 mg/kg/day for 8 weeks induced moderate but sustained increases in plasma PTH levels and marked increases in bone turnover (increase in both bone formation and resorption), with no net bone gain or loss. Combination of oral compound and 17β-estradiol by s.c. infusion also produced an increase in bone turnover, but the antiresorptive effect of estrogen led to a decrease in the extent of bone resorption associated with elevated PTH levels, resulting in a net increase in bone mass compared to ovariectomized controls or animals treated with either drug alone. Potentially useful for the treatment of osteoporosis.

SOURCES – NPS Pharmaceuticals; SmithKline Beecham.

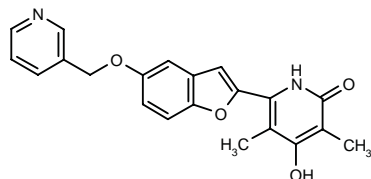
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2. Nemeth, E.F. et al. *Stimulation of parathyroid hormone secretion by a small molecule antagonist of the calcium receptor.* 2nd Jt Meet Am Soc Bone Miner Res Int Bone Miner Soc (Dec 1-6, San Francisco) 1998, Abst 1030.

TREATMENT OF LIPOPROTEIN DISORDERS

289907

4-Hydroxy-3,5-dimethyl-6-[5-(3-pyridinylmethoxy)benzofuran-2-yl]pyridin-2(1H)-one



C21 H18 N2 O4; Mol wt: 362.3832

ACTION – Agent for the treatment of hyperlipidemia and atherosclerosis, a triglyceride biosynthesis inhibitor (31-68% inhibition at 0.125-0.5 μ M in HepG2 cells) proven to decrease triglyceride levels by 72.1% and to increase the HDL/total cholesterol ratio by 68% at 30 mg/kg/day p.o. x 7 days in rats. A representative compound from a series of benzofuryl- α -pyridone derivatives.

SOURCES – Microbial Chemistry Research Foundation, Tokyo (JP); Teijin.

REFERENCES

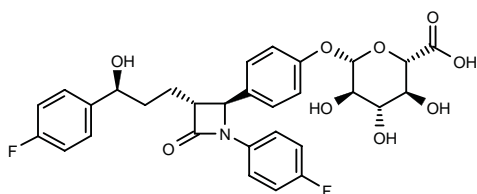
1. Ida, T. et al. (Teijin Ltd.; Microbial Chemistry Research Foundation) *Benzofuryl- α -pyridone derivs.* JP 2000128878.

SCH-60663

289944

1-O-[4-[(2S,3R)-1-(4-Fluorophenyl)-3-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidiny]phenyl]- β -D-glucopyranosiduronic acid

Ezetimibe glucuronide



C30 H29 F2 N O9; Mol wt: 585.5531

ACTION – Cholesterol absorption inhibitor, a phenolic glucuronide of the potent and selective inhibitor of intestinal cholesterol absorption Sch-58235 (ezetimibe), proven to be more potent than the parent compound in rats when given by the intraduodenal route. The glucuronidation of Sch-58235 appears to improve activity because the drug is repeatedly delivered back to the site of action via enterohepatic circulation and the residence time in the gut is increased.

SOURCE – Schering-Plough.

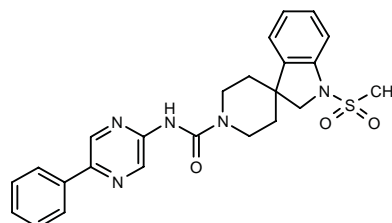
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TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

289950

1-(Methanesulfonyl)-N-(5-phenylpyrazin-2-yl)spiro-[indoline-3,4'-piperidine]-1'-carboxamide



C24 H25 N5 O3 S; Mol wt: 463.5595

ACTION – Neuropeptide Y (NPY) Y_5 receptor antagonist that inhibits obsessive food intake and is therefore potentially useful for the treatment of obesity and the complications associated therewith. It was demonstrated to dose-dependently suppress bovine pancreatic polypeptide-induced food intake in male rats at doses of 1, 3, 10 and 30 mg/kg administered orally by gavage, with the minimum effective dose estimated to be 3 mg/kg. The compound did not cause any abnormal behavior in rats and mice during 24 h after dosing at 100 mg/kg p.o.

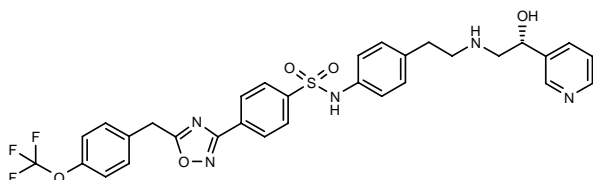
SOURCE – Merck & Co.

REFERENCES

1. Gao, Y.-D. et al. (Merck & Co., Inc.; Banyu Pharmaceutical Co., Ltd.) *Spiro-indolines as Y_5 receptor antagonists.* WO 0027845.

291270

N-[4-[2-[2(*R*)-Hydroxy-2-(3-pyridyl)ethylamino]ethyl]-phenyl]-4-[5-[4-(trifluoromethoxy)benzyl]-1,2,4-oxadiazol-3-yl]benzenesulfonamide



C31 H28 F3 N5 O5 S; Mol wt: 639.6522

ACTION – Potent β_3 -adrenoceptor agonist (EC_{50} = 8 nM for adenylyl cyclase activation) with high selectivity over β_1 - and β_2 -adrenoceptors (IC_{50} = 1290 and 7600 nM, respectively, for displacement of [125 I]-iodocyanopindolol binding from membranes of CHO cells expressing human receptors). Compound showed good oral bioavailability (30%) and a half-life of 3.8 h in dogs. In anesthetized rhesus monkeys, it produced dose-dependent glycerolemia (ED_{50} = 0.15 mg/kg) with minimal increases in heart rate at much higher doses (15% at 10 mg/kg). Potentially useful for the treatment of obesity and diabetes.

SOURCE – Merck & Co.

REFERENCES

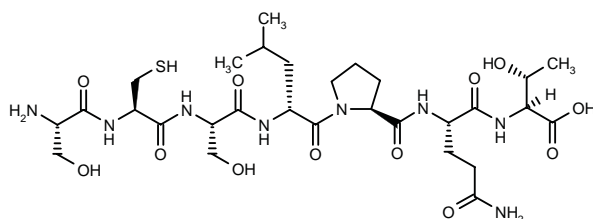
1. Biftu, T. et al. (Merck & Co., Inc.) Oxadiazole benzenesulfonamides as selective β_3 agonists for the treatment of diabetes and obesity. EP 0906310, US 6034106, WO 9746556.

2. Biftu, T. et al. Synthesis and SAR of benzyl and phenoxymethylene oxadiazole benzenesulfonamides as selective β_3 adrenergic receptor agonist antiobesity agents. Bioorg Med Chem Lett 2000, 10(13): 1431.

[D-Leu⁴]-OB3

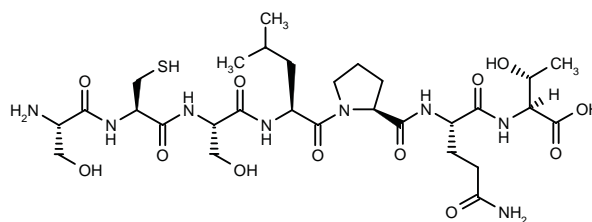
290986

L-Seryl-L-cysteinyl-L-seryl-D-leucyl-L-prolyl-L-glutaminyl-L-threonine



C29 H50 N8 O12 S; Mol wt: 734.8240

ACTION – Antiobesity agent, a derivative of the synthetic leptin agonist **OB3** proven to be much more effective than the parent compound in reducing food intake and body weight in *ob/ob* mice after treatment with a dose of 1 mg/kg/day i.p. for 7 days. Unlike native leptin, however, neither OB3 nor its D-amino acid-substituted analogue had any apparent effect on thermogenesis.



OB3 [290769]: C29 H50 N8 O12 S

SOURCE – Albany Medical College, Albany, NY (US).

REFERENCES

1. Grasso, P. et al. (Albany Medical College) Leptin-related peptides. WO 0011173.

2. Rozhavskaya-Arena, M. et al. Design of a synthetic leptin agonist: D-Amino acid substitution of residues 116 to 122 of mouse leptin. 82nd Annu Meet Endocr Soc (June 21-24, Toronto) 2000, Abst 1207.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

289734

L-Ile-L-Glu-Gly-L-Pro-L-Thr-L-Leu-L-Arg-L-Gln-L-Trp-L-Leu-L-Ala-L-Ala-L-Arg-L-Ala-Gly-Gly-L-(S-polyethylene glycol)-Cys-Gly-Gly-L-Ile-L-Glu-L-Pro-L-Thr-L-Leu-L-Arg-L-Gln-L-Trp-L-Leu-L-Ala-L-Ala-L-Arg-L-Ala

C161 H260 N52 O46 S(C2 H4 O)_n; Mol wt: 3736.2620

ACTION – Thrombopoietic agent that is thought to exert its activity by binding to the endogenous thrombopoietin (TPO) receptor c-Mpl. When administered to mice using osmotic minipumps, compound was found to be about 10-fold more potent than unpegylated recombinant human megakaryocyte growth and development factor (MGDF), with maximal effects being observed at 100 μ g/kg/day.

SOURCE – Amgen.

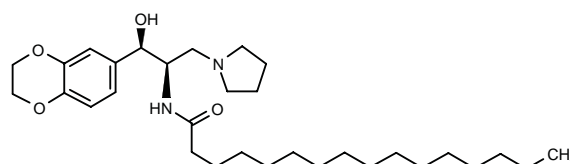
REFERENCES

1. Liu, C.-F. et al. (Amgen Inc.) Thrombopoietic cpds. WO 0024770.

THERAPY OF INBORN ERRORS OF METABOLISM

290120

N-[(1*R*,2*R*)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-hydroxy-1-(1-pyrrolidinylmethyl)ethyl]hexadecanamide



C31 H52 N2 O4; Mol wt: 516.7618

ACTION – Glucosylceramide synthase inhibitor for use in the treatment of Fabry's disease. In wild-type mice, compound was shown to produce dose-dependent (0.1-10 mg/kg i.p. every 12 h for 3 days) reductions in kidney, liver and spleen glucosylceramide content, with a 75-80% reduction in all tissues at the highest dose. In α -galactosidase A (α -gal A) knockout mice, a model of Fabry's disease, compound given for 4 or 8 weeks twice daily at doses of 2-30 mg/kg significantly reduced globotriaosylceramide content in the kidney and liver compared to controls; the levels in the kidney at doses of 10 or 15 mg/kg were reduced to below baseline levels. Unlike the known glucosylceramide synthase inhibitor *N*-butyldeoxynojirimycin, it did not induce toxic effects on behavior or body weight.

SOURCES – University of Michigan, Ann Arbor, MI (US); National Institutes of Health, Bethesda, MD (US).

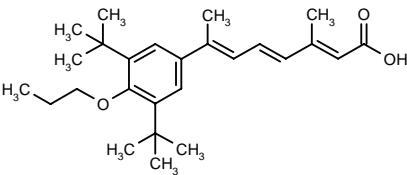
REFERENCES

1. Abe, A. et al. *Reduction of globotriaosylceramide in Fabry disease mice by substrate deprivation.* J Clin Invest 2000, 105(10): 1563.
2. Lee, L. et al. *Improved inhibitors of glucosylceramide synthase.* J Biol Chem 1999, 274(21): 14662.

TREATMENT OF POISONING,
DRUG ABUSE AND DEPENDENCY

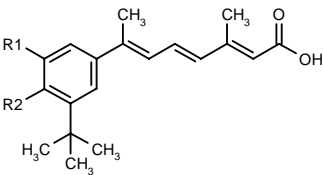
289751

7-(3,5-Di-*tert*-butyl-4-propoxyphenyl)-3-methyl-2(*E*), 4(*E*),6(*E*)-octatrienoic acid



C26 H38 O3; Mol wt: 398.5832

ACTION – Selective retinoic acid receptor (RAR) antagonist, as demonstrated in binding assays by K_d values of 2, 1 and 4 nM, respectively, for RAR α , RAR β and RAR γ receptors as compared to K_d values > 10 μ M for retinoid X receptors RXR α , RXR β and RXR γ . Potentially useful in the treatment of hypervitaminosis A syndrome and as an adjunct to RAR agonist therapy to prevent the occurrence of one or more of the associated side effects. Other specifically claimed compounds from this series of trienoic retinoid compounds are:



Compound	R1	R2	Formula
289752	t-Bu	OBu	C ₂₇ H ₄₀ O ₃
289754	t-Bu	OC5H11	C ₂₈ H ₄₂ O ₃
289755	t-Bu	OC6H13	C ₂₉ H ₄₄ O ₃
289756	t-Bu	OC7H15	C ₃₀ H ₄₆ O ₃
289758	t-Bu	OC8H17	C ₃₁ H ₄₈ O ₃
289759	C(Ph)=CH2	H	C ₂₇ H ₃₀ O ₂
289761	t-Bu	O(CH2)3CHDCH2D	C ₂₈ H ₄₀ O ₃ D ₂

SOURCE – Ligand.

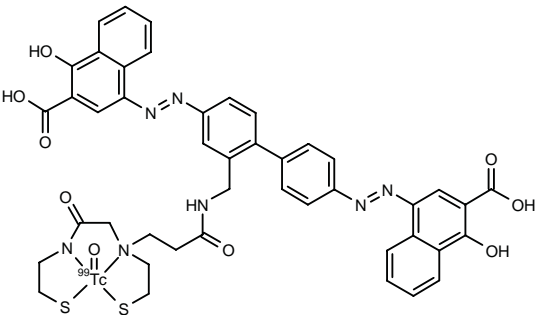
REFERENCES

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DIAGNOSTIC AGENTS

288855

Dihydrogen (*SP-5-35*)-[[4,4'-[[2-[[[3-[[2-(mercapto- κ S)-ethyl][2-[[2-(mercapto- κ S)ethyl]amino- κ N]-2-oxoethyl]-amino- κ N]-1-oxopropyl]amino]methyl][1,1'-biphenyl]-4,4'-diyl]bis(azo)]bis[1-hydroxy-2-naphthalenecarboxylato]]-(5-)]oxotechnetate(2-)-⁹⁹Tc



C44 H48 N7 O9 S2 Tc ; Mol wt: 971.9562

ACTION – Organometallic ligand that interacts with amyloid fibrils and is therefore useful for the diagnosis and treatment of Alzheimer's disease. The labeled ligand allows the localization and quantification of amyloid fibrils to determine the degree of progression of the disease. Other specifically claimed compounds are:

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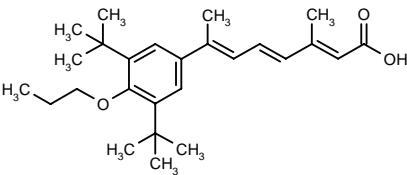
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DRUG ABUSE AND DEPENDENCY

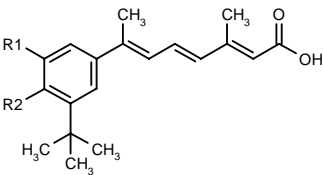
289751

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SOURCE – Ligand.

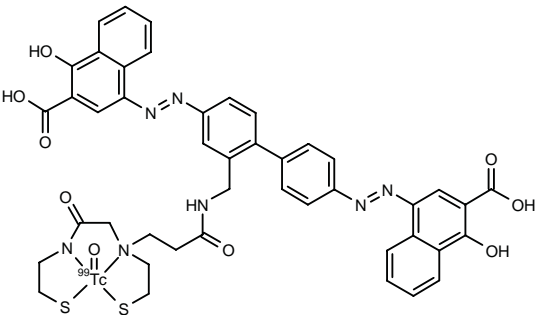
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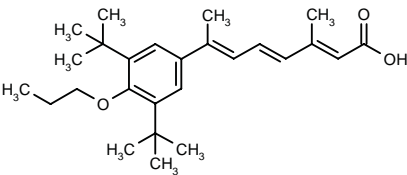
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TREATMENT OF POISONING,
DRUG ABUSE AND DEPENDENCY

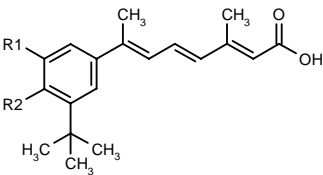
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289755	t-Bu	OC6H13	C ₂₉ H ₄₄ O ₃
289756	t-Bu	OC7H15	C ₃₀ H ₄₆ O ₃
289758	t-Bu	OC8H17	C ₃₁ H ₄₈ O ₃
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SOURCE – Ligand.

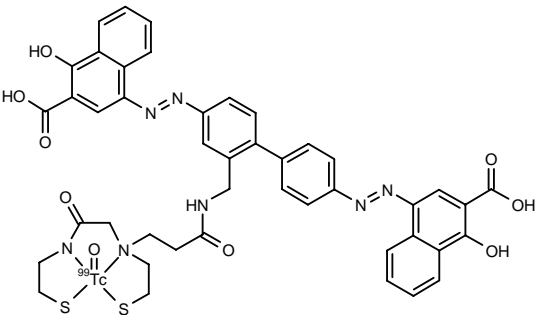
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DIAGNOSTIC AGENTS

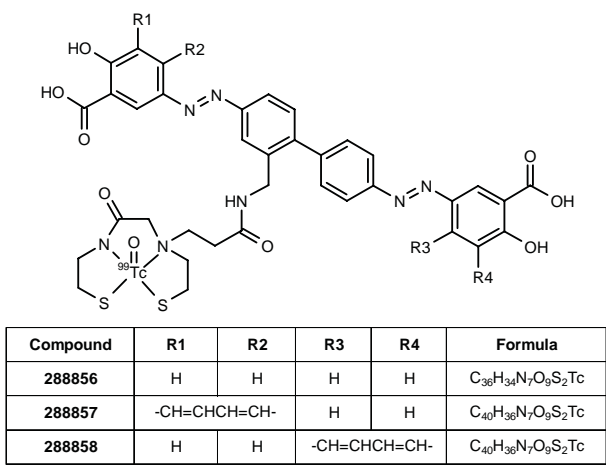
288855

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C44 H48 N7 O9 S2 Tc ; Mol wt: 971.9562

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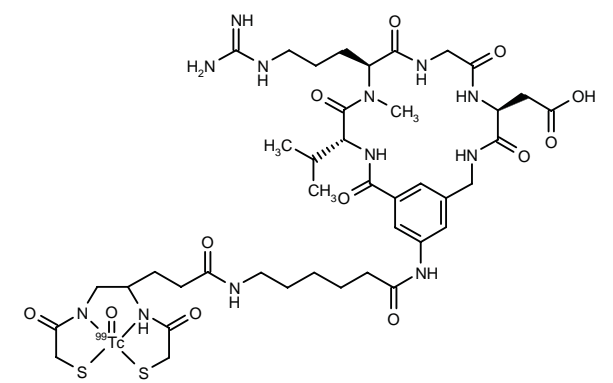
SOURCE – Massachusetts Institute of Technology, Cambridge, MA (US).

REFERENCES

1. Lansbury, P.T. Jr. et al. (Massachusetts Institute of Technology) *Organometallic ligands for the localization and quantification of amyloid in vivo and in vitro*. US 6054114.

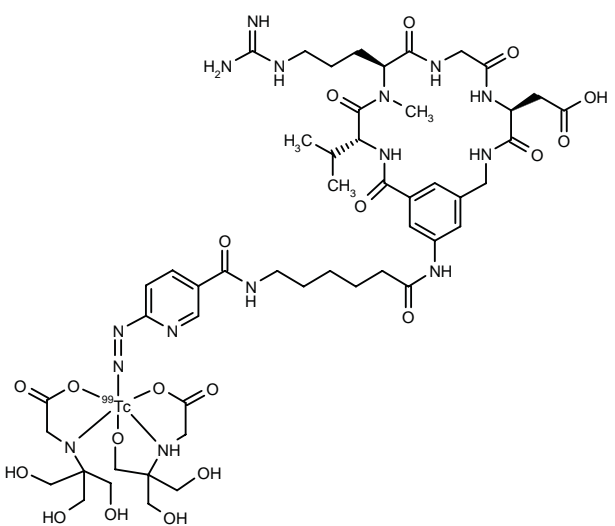
288892

Dihydrogen [cyclo[*N*²-methyl-L-arginyl-glycyl-L-aspartyl-3-(aminomethyl)-5-[[6-[[3-[[1,2-bis[[2-(mercapto-κ*S*)-1-oxoethyl]amino-κ*M*]ethyl]-1-oxopropyl]amino]-1-oxohexyl]amino]benzoyl-D-valyl]ato(5-)]oxotechnetate-(2-)-⁹⁹Tc



C41 H61 N12 O12 S2 Tc ; Mol wt: 1077.1370

ACTION – A representative compound from a series of radiolabeled cyclic compounds containing carbocyclic or heterocyclic ring systems and acting as fibrinogen gpIIb/IIIa antagonists for use as imaging agents for the diagnosis of thromboembolic disorders. Compound exhibited a good ability to incorporate into thrombi when tested in canine models of arteriovenous shunt and deep vein thrombosis. Another exemplified compound is:



288898: C50 H74 N15 O19 Tc

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. DeGrado, W.F. et al. (DuPont Pharmaceuticals Co.) *Radiolabeled platelet GPIIb/IIIa receptor antagonists as imaging agents for the diagnosis of thromboembolic disorders*. EP 0995761.

289663

[*N,N',N'',N''',N''''',N'''''*-(Benzene-1,3,5-triyl)tris-[carbonylnitrilodi(2,1-ethanediyl)]hexakis[*N*²,*N*⁶-bis[*N*²,*N*⁶-[*N*-[2-[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododec-1-yl]propionyl]glycyl]lysyl]lysineamide]]tetracosagadolium

C585 H928 Gd24 N165 O213 ; Mol wt: 17454.7100

ACTION – A representative compound from a series of cascade polymer complexes useful as contrast agents for NMR or X-ray diagnostic techniques; these compounds possess the advantage over extracellular contrast media such as Gd-DTPA that they are dispersed exclusively in the vascular space (blood pool agents) and are thus useful for the visualization of vessels, for example for the diagnosis of ischemia and regions with high vascular permeability such as tumors.

SOURCE – Schering AG.

REFERENCES

1. Schmitt-Willich, H. et al. (Schering AG) *Cascade polymer complexes, process for their production and pharmaceutical agents containing said complexes*. US 6063361.

290055

L-Methionyl-L-threonyl-L-glutamyl-L-glutaminyl-L-glutaminyl-L-tryptophyl-L-asparaginyll-L-phenylalanyl-L-alanyl-glycyl-L-isoleucyl-L-glutamyl-L-alanyl-L-alanyl-L-alanine

C73 H107 N19 O24 S; Mol wt: 1666.8230

ACTION – Peptide derived from the ESAT-6 protein of *Mycobacterium tuberculosis* that is recognized by the T-cells of a high proportion of tuberculosis patients, in particular 57% of tuberculosis patients tested and 68% of healthy volunteers that had been exposed to open pulmonary tuberculosis, and can thus be used as the basis of a novel diagnostic test. This diagnostic assay offers the advantage over current tests such as the tuberculin skin test (TST) that BCG does not have the ESAT-6 gene and thus it allows to distinguish between patients with tuberculosis and patients vaccinated with BCG.

SOURCE – Isis Innovation.

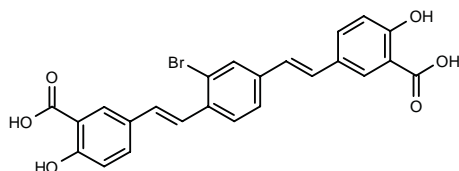
REFERENCES

1. Lalvani, A. and Pathan, A.A. (Isis Innovation Ltd.) *Tuberculosis diagnostic test*. WO 0026248.

BSB

290672

5-[(E)-2-[2-Bromo-4-[(E)-2-(3-carboxy-4-hydroxyphenyl)-vinyl]phenyl]vinyl]-2-hydroxybenzoic acid



C24 H17 Br O6; Mol wt: 481.2963

ACTION – Probe for the detection of amyloid plaque with high binding affinity for β -amyloid peptide ($A\beta$; $K_i = 0.4 \mu\text{M}$), excellent fluorescent properties and lipophilicity. In addition, compound sensitively and specifically labels senile plaque in postmortem Alzheimer's disease (AD) brain sections and enters living cells and specifically binds to $A\beta$ aggregates. In transgenic mice with AD, compound given intracerebrally was seen to label $A\beta$ plaques with high sensitivity and specificity, and after i.v. injection it crossed the blood–brain barrier and distributed throughout the brain. Potentially useful for radiological imaging of the brain of living patients for diagnosing AD, as well as for monitoring the progression of the disease or assessing the efficacy of clinical treatments.

SOURCE – University of Pennsylvania, Philadelphia, PA (US).

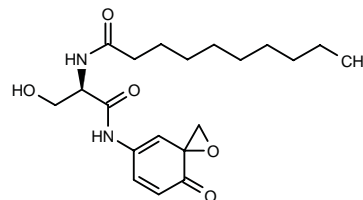
REFERENCES

1. Skovronsky, D.M. et al. *In vivo detection of amyloid plaques in a mouse model of Alzheimer's disease*. Proc Natl Acad Sci USA 2000, 97(13): 7609.

PHARMACOLOGICAL TOOLS

290688

N-[1(R)-(Hydroxymethyl)-2-oxo-2-(8-oxo-1-oxaspiro-[2.5]octa-4,6-dien-5-ylamino)ethyl]decanamide



C20 H30 N2 O5; Mol wt: 378.4660

ACTION – Selective and irreversible inhibitor of membrane-bound neutral sphingomyelinase (N-SMase; 25-100 μM), being inactive at up to 500 μM against lysosomal acid sphingomyelinase. Potentially useful as a pharmacological tool to elucidate the biological role of N-SMase on signal transduction processes.

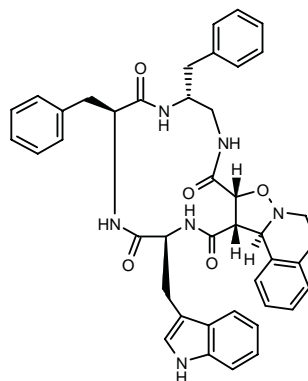
SOURCE – Universität Karlsruhe, Karlsruhe (DE).

REFERENCES

1. Arenz, C. and Giannis, A. *Synthesis of the first selective irreversible inhibitor of neutral sphingomyelinase*. Angew Chem. Int Ed Engl 2000, 39(8): 1440.

291168

(8aR,12R,15S,18S,20aS,20bR)-12,15-Dibenzyl-18-(1H-indol-3-ylmethyl)-5,8a,10,11,12,13,15,16,18,19,20a,20b-dodecahydro-6H-[1,4,7,10]tetraazacyclotetradecino-[12',13':4,5]isoxazolo[3,2-a]isoquinoline-9,14,17,20-tetraone



C42 H42 N6 O5; Mol wt: 710.8308

M.p. 173-5 °C.

ACTION – Potent human tachykinin NK_2 receptor ligand ($pK_i = 8.7$) with superior affinity compared to the bicyclic peptide MEN-10627 ($pK_i = 8.0$). Another related compound is:

290055

L-Methionyl-L-threonyl-L-glutamyl-L-glutaminyl-L-glutaminyl-L-tryptophyl-L-asparaginyll-L-phenylalanyl-L-alanyl-glycyl-L-isoleucyl-L-glutamyl-L-alanyl-L-alanyl-L-alanine

C73 H107 N19 O24 S; Mol wt: 1666.8230

ACTION – Peptide derived from the ESAT-6 protein of *Mycobacterium tuberculosis* that is recognized by the T-cells of a high proportion of tuberculosis patients, in particular 57% of tuberculosis patients tested and 68% of healthy volunteers that had been exposed to open pulmonary tuberculosis, and can thus be used as the basis of a novel diagnostic test. This diagnostic assay offers the advantage over current tests such as the tuberculin skin test (TST) that BCG does not have the ESAT-6 gene and thus it allows to distinguish between patients with tuberculosis and patients vaccinated with BCG.

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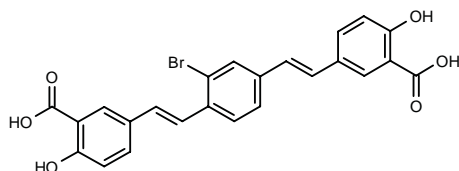
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BSB

290672

5-[(E)-2-[2-Bromo-4-[(E)-2-(3-carboxy-4-hydroxyphenyl)-vinyl]phenyl]vinyl]-2-hydroxybenzoic acid



C24 H17 Br O6; Mol wt: 481.2963

ACTION – Probe for the detection of amyloid plaque with high binding affinity for β -amyloid peptide ($A\beta$; $K_i = 0.4 \mu\text{M}$), excellent fluorescent properties and lipophilicity. In addition, compound sensitively and specifically labels senile plaque in postmortem Alzheimer's disease (AD) brain sections and enters living cells and specifically binds to $A\beta$ aggregates. In transgenic mice with AD, compound given intracerebrally was seen to label $A\beta$ plaques with high sensitivity and specificity, and after i.v. injection it crossed the blood–brain barrier and distributed throughout the brain. Potentially useful for radiological imaging of the brain of living patients for diagnosing AD, as well as for monitoring the progression of the disease or assessing the efficacy of clinical treatments.

SOURCE – University of Pennsylvania, Philadelphia, PA (US).

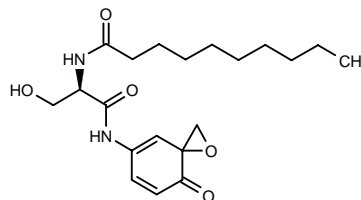
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1. Skovronsky, D.M. et al. *In vivo detection of amyloid plaques in a mouse model of Alzheimer's disease*. Proc Natl Acad Sci USA 2000, 97(13): 7609.

PHARMACOLOGICAL TOOLS

290688

N-[1(R)-(Hydroxymethyl)-2-oxo-2-(8-oxo-1-oxaspiro-[2.5]octa-4,6-dien-5-ylamino)ethyl]decanamide



C20 H30 N2 O5; Mol wt: 378.4660

ACTION – Selective and irreversible inhibitor of membrane-bound neutral sphingomyelinase (N-SMase; 25-100 μM), being inactive at up to 500 μM against lysosomal acid sphingomyelinase. Potentially useful as a pharmacological tool to elucidate the biological role of N-SMase on signal transduction processes.

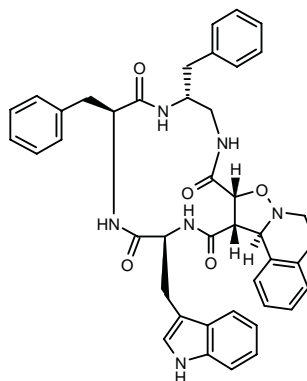
SOURCE – Universität Karlsruhe, Karlsruhe (DE).

REFERENCES

1. Arenz, C. and Giannis, A. *Synthesis of the first selective irreversible inhibitor of neutral sphingomyelinase*. Angew Chem. Int Ed Engl 2000, 39(8): 1440.

291168

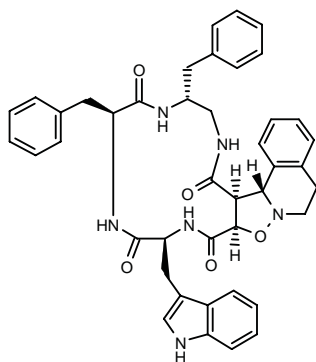
(8aR,12R,15S,18S,20aS,20bR)-12,15-Dibenzyl-18-(1H-indol-3-ylmethyl)-5,8a,10,11,12,13,15,16,18,19,20a,20b-dodecahydro-6H-[1,4,7,10]tetraazacyclotetradecino-[12',13':4,5]isoxazolo[3,2-a]isoquinoline-9,14,17,20-tetraone



C42 H42 N6 O5; Mol wt: 710.8308

M.p. 173-5 °C.

ACTION – Potent human tachykinin NK_2 receptor ligand ($pK_i = 8.7$) with superior affinity compared to the bicyclic peptide MEN-10627 ($pK_i = 8.0$). Another related compound is:



291167: C42 H42 N6 O5

SOURCE – Menarini.

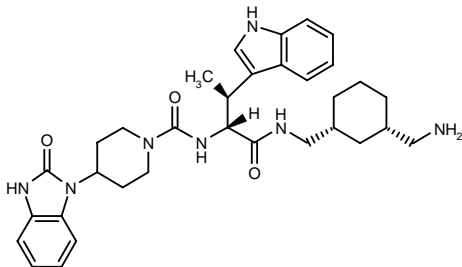
REFERENCES

1. Valenza, S. et al. *Regio- and stereoselective cycloadditions of cyclic nitrones to maleic diamide forced in a peptide: Synthesis of potent ligands of human NK-2 receptor.* J Org Chem 2000, 65(13): 4003.

L-779976*

269873

*N*¹-[3(*S*)-(Aminomethyl)-1(*R*)-cyclohexylmethyl]-*N*²-[4-(2-oxobenzimidazolin-1-yl)piperidin-1-ylcarbonyl]-3(*S*)-methyl-D-tryptophanamide



C33 H43 N7 O3; Mol wt: 585.7487

ACTION – Nonpeptide somatostatin sst2 receptor agonist with high affinity for the human sst2 receptor ($K_i = 0.05$ nM) and high selectivity relative to other human somatostatin receptor subtypes ($K_i = 2760, 729, 310$ and 4260 nM, respectively, for sst1, sst3, sst4 and sst5 receptors). Compound exhibited strong agonist activity in *in vitro* functional assays including inhibition of forskolin-stimulated cAMP production in CHO-K1 cells expressing sst2 receptor ($IC_{50} = 0.05$ nM), inhibition of growth hormone secretion from rat pituitary cells ($IC_{50} = 0.025$ nM) and inhibition of arginine-stimulated glucagon secretion from mouse pancreatic islet cells ($IC_{50} = 0.1$ nM). Inhibition of insulin secretion from mouse pancreatic islets required a 1,000-fold higher concentration ($IC_{50} = 100$ nM). Potentially useful as a pharmacological tool for elucidating the physiological functions of the sst2 receptor.

SOURCE – Merck & Co.

REFERENCES

1. Yang, L. et al. (Merck & Co., Inc.) *Somatostatin agonists.* EP 1023061, US 6057338, WO 9844921.
2. Berk, S.C. et al. *A combinatorial approach toward the discovery of non-peptide, subtype-selective somatostatin receptor ligands.* J Com Chem 1999, 1(5): 388.
3. Rohrer, S.P. et al. *Rapid identification of subtype-selective agonists of the somatostatin receptor through combinatorial chemistry.* Science 2000, 282(5389): 737.
4. Strowski, M.Z. et al. *Somatostatin inhibits insulin and glucagon secretion via two receptor subtypes: An in vitro study of pancreatic islets from somatostatin receptor 2 knockout mice.* Endocrinology 2000, 141(1): 111.
5. Wilson, S.H. et al. *Involvement of ERK, CDK and caspases in human retinal endothelial cell apoptosis induced by the somatostatin analogue L779,976.* 82nd Annu Meet Endocr Soc (June 21-24, Toronto) 2000, Abst 1067.

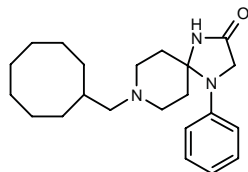
*Identified compound **269873** (see **269871**) Drug Data Rep 1999, 021(01): 0048.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

291021

8-(Cyclooctylmethyl)-4-phenyl-1,4,8-triazaspiro[4.5]-
decan-2-one



C₂₂ H₃₃ N₃ O; Mol wt: 355.5227

ACTION – A representative compound from a series of 4-oxoimidazolidine-2-spiro-nitrogenated heterocyclic derivatives acting as ORL1 (N/OFQ, nociceptin) receptor antagonists, with potential in the treatment of a broad range of diseases such as pain, obesity, Alzheimer's disease, schizophrenia, Parkinson's disease, depression, diabetes, polyuria and hypotension. *In vitro*, compound inhibited [¹²⁵I]-Tyr¹⁴-nociceptin binding to human ORL1 receptors expressed in CHO cells (IC₅₀ = 2.6 nM) and antagonized nociceptin-induced G-protein activation in these cells (IC₅₀ = 27 nM).

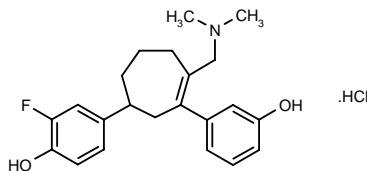
SOURCE – Banyu.

REFERENCES

1. Satoh, A. et al. (Banyu Pharmaceutical Co., Ltd.) 4-Oxoimidazolidine-2-spiro-nitrogenous heterocycle cpds.. WO 0034280.

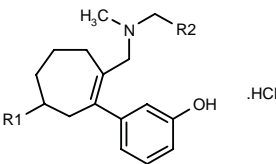
291032

4-[4-(Dimethylaminomethyl)-3-(3-hydroxyphenyl)-3-cyclohepten-1-yl]-2-fluorophenol hydrochloride



C₂₂ H₂₆ F N O₂ . HCl; Mol wt: 391.9113

ACTION – Analgesic agent, a delta opioid (DOP) receptor agonist (K_i = 14.6 ± 2.2 nM) active in the phenylquinone-induced writhing test in mice (ED₅₀ = 0.89 mg/kg i.v.). Other exemplified substituted cycloheptenes include the following:



Compound	R1	R2	Formula
291033	3-OH-Ph	H	C ₂₂ H ₂₇ NO ₂ .HCl
291034	4-Cl-Ph	H	C ₂₂ H ₂₆ ClNO.HCl
291035	Ph	H	C ₂₂ H ₂₇ NO.HCl
291036	1-Naph	H	C ₂₆ H ₂₉ NO.HCl
291037	2-Naph	H	C ₂₆ H ₂₉ NO.HCl
291038	4-OH-Ph	H	C ₂₂ H ₂₇ NO ₂ .HCl
291039	6-OH-2-Naph	H	C ₂₆ H ₂₉ NO ₂ .HCl
291040	Ph	CH ₂ Ph	C ₂₉ H ₃₃ NO.HCl

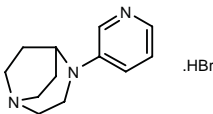
SOURCE – Grünenthal.

REFERENCES

1. Zimmer, O. et al. (Grünenthal GmbH) Substd. cycloheptenes, their preparation and use. DE 19857475, EP 1010689, JP 2000178238.

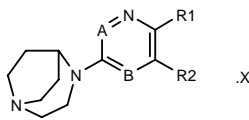
291091

4-(3-Pyridinyl)-1,4-diazabicyclo[3.2.2]nonane
hydrobromide



C₁₂ H₁₇ N₃ . HBr; Mol wt: 284.1992

ACTION – Agent with affinity for nicotinic acetylcholine receptors, potentially useful as an analgesic, particularly for acute neuropathic pain, as well as for CNS or gastrointestinal disorders related to nicotinic receptor dysfunction including cognition disorders, Parkinson's disease, neurodegenerative diseases, psychiatric disorders, Crohn's disease, ulcerative colitis, irritable bowel syndrome and obesity. Other exemplified 1,4-diazabicyclo[3.2.2]nonane derivatives include the following:



Compound	R1	R2	A	B	X	Formula
291092	Cl	H	N	CH	HBr	C ₁₁ H ₁₅ ClN ₄ .HBr
291093	Ph	H	CH	CH	HBr	C ₁₈ H ₂₁ N ₃ .HBr
291094	H	Br	CH	CH	HBr	C ₁₂ H ₁₆ BrN ₃ .HBr
291095	H	Ph	CH	CH		C ₁₈ H ₂₁ N ₃
291096	H	Cl	CH	N		C ₁₁ H ₁₅ ClN ₄
291097	Ph	H	N	CH	HBr	C ₁₇ H ₂₀ N ₄ .HBr

Certain compounds of the invention are selective ligands for the $\alpha 4\beta 2$, $\alpha 7$ or $\alpha 3$ subunits of the nicotinic acetylcholine receptor, while others are mixed $\alpha 4\beta 2$ and $\alpha 7$ or $\alpha 4\beta 2$ and $\alpha 3$ ligands.

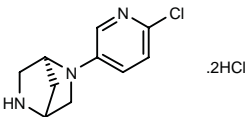
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Lochead, A. et al. (Sanofi-Synthélabo) *1,4-Diazabicyclo[3.2.2]nonane derivs., their preparation and therapeutic application.* FR 2786770, WO 0034279.

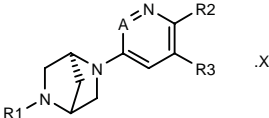
291098

1(S)-2-(6-Chloropyridin-3-yl)-2,5-diazabicyclo[2.2.1]-heptane dihydrochloride



C10 H12 Cl N3 . 2HCl; Mol wt: 282.6006

ACTION – Agent with affinity for nicotinic acetylcholine receptors, potentially useful as an analgesic, particularly for acute neuropathic pain, as well as for CNS or gastrointestinal disorders related to nicotinic receptor dysfunction including cognition disorders, Parkinson’s disease, neurodegenerative diseases, psychiatric disorders, Crohn’s disease, ulcerative colitis, irritable bowel syndrome and obesity. Other exemplified 2,5-diazabicyclo[2.2.1]heptane derivatives include the following:



Compound	R1	R2	R3	A	X	Formula
291099	Me	Cl	H	CH	fumarate	C ₁₁ H ₁₄ ClN ₃ .C ₄ H ₄ O ₄
291100	Me	Cl	H	N	.2HCl	C ₁₀ H ₁₃ ClN ₄ .2HCl
291101	H	Ph	H	N		C ₁₅ H ₁₆ N ₄
291102	Me	Ph	H	N		C ₁₆ H ₁₈ N ₄
291103	H	H	Ph	CH		C ₁₆ H ₁₇ N ₃
291104	H	Ph	H	CH		C ₁₆ H ₁₇ N ₃

Certain compounds of the invention are selective ligands for the $\alpha 4\beta 2$, $\alpha 7$ or $\alpha 3$ subunits of nicotinic acetylcholine receptors, while others are mixed $\alpha 4\beta 2$ and $\alpha 7$ or $\alpha 4\beta 2$ and $\alpha 3$ ligands.

SOURCE – Sanofi-Synthélabo.

REFERENCES

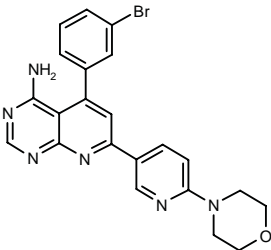
1. Lochead, A. et al. (Sanofi-Synthélabo) *2,5-Diazabicyclo[2.2.1]heptane derivs., their preparation and therapeutic uses.* FR 2786769, WO 0034284.

ABT-702*

289331

5-(3-Bromophenyl)-7-[6-(4-morpholinyl)pyridin-3-yl]-pyrido[2,3-*d*]pyrimidin-4-amine

5-(3-Bromophenyl)-7-[6-(4-morpholinyl)pyridin-3-yl]-pyrido[2,3-*d*]pyrimidin-4-ylamine



C22 H19 Br N6 O; Mol wt: 463.3371

ACTION – Nonopioid analgesic and antiinflammatory agent, a potent, competitive and reversible non-nucleoside adenosine kinase inhibitor (IC₅₀ = 1 nM) with high selectivity over other sites of adenosine interaction, as well as a panel of neurotransmitter and peptide receptors, ion channels, proteins, reuptake sites and enzymes. Compound is orally available and showed very strong analgesic activity in a series of preclinical models of pain in rats, including thermal nociceptive pain, carrageenan-induced thermal hyperalgesia, the formalin test and neuronal pain induced by nerve injury and diabetes. Compound is particularly effective in relieving inflammatory pain (ED₅₀ = 5 μ mol/kg p.o.) and is also active in acute models of inflammation. At analgesic doses, it did not affect motor coordination, heart rate, blood pressure or body temperature.

SOURCE – Abbott.

REFERENCES

1. Bhagwat, S.S. et al. (Abbott Laboratories Inc.) *5,7-Disubstd.-4-aminopyrido[2,3-d]-pyrimidine cpds. and their use as adenosine kinase inhibitors.* EP 0989986, WO 9846605.

2. Bhagwat, S.S. et al. (Abbott Laboratories Inc.) *5,7-Disubstd.-4-aminopyrido[2,3-d]-pyrimidine cpds.* WO 0023444.

3. Kowaluk, E.A. et al. *ABT-702, a novel orally effective adenosine kinase (AK) inhibitor analgesic with anti-inflammatory properties.* Drug Dev Res 2000, 50(1): Abst 222.

4. Lee, C. et al. *Structure-activity relationship of a series of novel, non-nucleoside analogs as adenosine kinase inhibitors.* Drug Dev Res 2000, 50(1): Abst 056.

*Identified compound **289331** Drug Data Rep 2000, 022(08): 0678.

CONTULAKIN G¹⁻³

285840

L-Pyroglutamyl-L-seryl-L-glutamyl-L-glutamyl-glycyl-glycyl-L-seryl-L-asparaginy-L-alanyl-O[2-acetamido-2-deoxy-3-(β-D-galactopyranosyl)-α-D-galactopyranosyl]-L-threonyl-L-lysyl-L-lysyl-L-prolyl-L-tyrosyl-L-isoleucyl-L-leucine

CGX-1160

C88 H140 N20 O37; Mol wt: 2070.1770

ACTION – Conopeptide isolated from the venom of *Conus geographus*, a member of the neurotensin family of peptides with neurotensin receptor (NTR)-modulating activity. Compound competed for binding to the neurotensin receptor subtypes NTR1 (IC₅₀ = 960 and 524 nM against human and rat NTR1 receptors, respectively), NTR2 and NTR3 (IC₅₀ = 730 and 250 nM against rat NTR2 and murine NTR3 receptors, respectively). In *in vitro* functional experiments, it exhibited potent agonist activity for the rat NTR1 receptor, as demonstrated by stimulation of inositol phosphate accumulation in CHO cells expressing rat NTR1 receptors. When tested *in vivo* in mice, compound exhibited potent analgesic activity in the tail-flick and formalin tests (ED₅₀ = 30-40 and 1 pmol i.t. in the first and second phases of the formalin test, respectively) and was shown to potently and dose-dependently reverse CFA-induced mechanical allodynia. Anticonvulsant activity was demonstrated by inhibition of audiogenic seizures in mice following i.c.v. administration (ED₅₀ = 7.1 pmol). Its desglycosylated analogue is:

L-Pyroglutamyl-L-seryl-L-glutamyl-L-glutamyl-glycyl-glycyl-L-seryl-L-asparaginy-L-alanyl-L-threonyl-L-lysyl-L-lysyl-L-prolyl-L-tyrosyl-L-isoleucyl-L-leucine

289323:^{1,2} C74 H117 N19 O27

SOURCE – Cognetix.

REFERENCES

1. Craig, A.G. et al. (Cognetix, Inc.;The Salk Institute for Biological Studies;University of Utah) *Contulakin-G, analogs thereof and uses therefor*. WO 0023092.

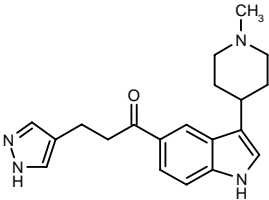
2. Craig, A.G. et al. *Contulakin-G, an O-glycosylated invertebrate neurotensin*. J Biol Chem 1999, 274(20): 13752.

3. *Cognetix, Elan team up to develop novel analgesic/drug delivery system*. DailyDrugNews.com (Daily Essentials) 2000, Feb 4.

ANTIMIGRAINE DRUGS

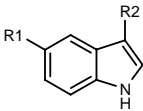
291236

1-[3-(1-Methylpiperidin-4-yl)-1*H*-indol-5-yl]-3-(1*H*-pyrazol-4-yl)propan-1-one



C20 H24 N4 O; Mol wt: 336.4366

ACTION – 5-ht_{1F} receptor agonist for the treatment of migraine, with affinity for 5-ht_{1F} receptors when tested in radioligand binding assays and proven to act as an agonist at this receptor in a cAMP formation test. Other exemplified indole derivatives include the following:



Compound	R1	R2	Formula
291237	3-i-Pr-PhCOCH2	1-Me-1,2,3,6-tetrahydro-4-Pyr	C ₂₅ H ₂₈ N ₂ O
291238	2-Br-PhCOCH2	1-Me-4-Pip	C ₂₂ H ₂₃ BrN ₂ O
291239	2-F-PhCOCH2	octahydro-6-indoliziny	C ₂₄ H ₂₅ FN ₂ O
291240	3-Cl-PhCOCH2	1-Me-2-pyrrolidinyl-CH2	C ₂₂ H ₂₃ ClN ₂ O
291241	2,3-(I)2-PhCOCH2	1-Me-1,2,3,6-tetrahydro-4-Pyr	C ₂₂ H ₂₀ I ₂ N ₂ O
291242	2,4-(NH2)2-Ph-COCH2	1-Me-2-pyrrolidinyl-CH2	C ₂₂ H ₂₆ N ₄ O
291243	2-Me-PhCOCH2	octahydro-6-indoliziny	C ₂₅ H ₂₈ N ₂ O
291244	2,4-(Cl)2-PhCOCH2	1-Me-1,2,3,6-tetrahydro-4-Pyr	C ₂₂ H ₂₀ Cl ₂ N ₂ O
291246	3-thienyl-CH2CH2CO	1-Me-4-Pip	C ₂₁ H ₂₄ N ₂ OS

SOURCE – Lilly.

REFERENCES

1. Schaus, J.M. and Xu, Y.-C. (Eli Lilly and Company) *Indole derivs. and their use as 5-HT_{1F} agonists*. WO 0034266.

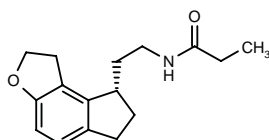
PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

TAK-375*

255673

(-)-(S)-N-[2-(2,6,7,8-Tetrahydro-1H-indeno[5,4-b]furan-8-yl)ethyl]propionamide



C₁₆ H₂₁ N O₂; Mol wt: 259.3469

ACTION – Potent melatonin ML₁ receptor agonist with high affinity for chick forebrain ML₁ receptors ($K_i = 25.4$ pM) and much lower affinity for hamster ML₂ receptors ($K_i = 2600$ nM). In *in vitro* functional experiments, compound inhibited forskolin-stimulated cAMP production in neonatal rat pituitary with an IC₅₀ of 98 pM, indicating that it acts as an ML₁ receptor agonist. No significant activity was seen at other receptors, ion channels or enzymes. *In vivo*, doses of 0.1-1 mg/kg p.o. promoted long-lasting sleep in freely moving cats, without inducing learning or memory impairment, motor dysfunction or drug dependence. In another study in freely moving monkeys, compound (0.03-0.3 mg/kg p.o.) increased total duration of sleep, especially the amount of slow-wave sleep, and exhibited a tendency to increase rapid eye movement (REM) sleep, inducing sleep qualitatively similar to spontaneous sleep, without adverse effects. Compound is currently undergoing clinical evaluation for the treatment of insomnia and circadian rhythm disorders.

SOURCE – Takeda.

REFERENCES

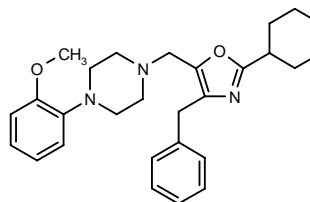
- Ohkawa, S. et al. (Takeda Chemical Industries, Ltd.) *Tricyclic cpds., their production and use*. EP 0885210, JP 1998287665, JP 1999152281, WO 9732871.
- Ohkawa, S. and Miyamoto, M. (Takeda Chemical Industries, Ltd.) *Pharmaceutical compsn. for treating or preventing sleep disorders*. WO 9963977.
- Kato, K. et al. *Neuropharmacological properties of TAK-375, a novel ML1-selective melatonin receptor agonist*. Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.03.130.
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- Ohkawa, S. et al. *Synthesis of a novel series of tricyclic indan derivatives as melatonin agonists*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-108.
- Yukuhiro, N. et al. *Effects of TAK-375, a novel melatonin receptor agonist, on sleep in freely moving monkeys*. Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.03.127.

*Identified compound **255673** Drug Data Rep 1998, 020(01): 0016.

ANXIOLYTICS

292672

1-(4-Benzyl-2-cyclohexyloxazol-5-ylmethyl)-4-(2-methoxyphenyl)piperazine



C₂₈ H₃₅ N₃ O₂; Mol wt: 445.6035

ACTION – Potent 5-HT_{1A} receptor agonist with sub-nanomolar affinity ($K_i = 0.88$ nM) and high selectivity over dopamine D₂ receptors and α_1 -adrenoceptors ($K_i > 100$ nM). Compound exhibited functional agonist activity, as demonstrated by its ability to inhibit forskolin-induced cAMP turnover (EC₅₀ = 9 nM) in CHO cells stably transfected with the human 5-HT_{1A} receptor. Potentially useful for the treatment of psychopathological diseases including anxiety and depression.

SOURCE – Wyeth-Ayerst.

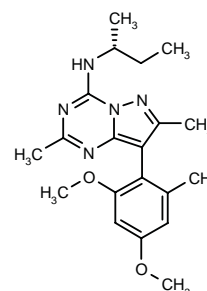
REFERENCES

- Greenblatt, L.P. et al. *Novel trisubstituted oxazole derivatives as 5-HT_{1A} receptor ligands*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 117.

IL-488

292387

8-(2,4-Dimethoxy-6-methylphenyl)-2,7-dimethyl-N-[1(R)-methylpropyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine



C₂₀ H₂₇ N₅ O₂; Mol wt: 369.4663

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist, a mixture of atropoisomers with high affinity for human and rat CRF receptors and potential use as an anxiolytic.

SOURCE – DuPont Pharmaceuticals.

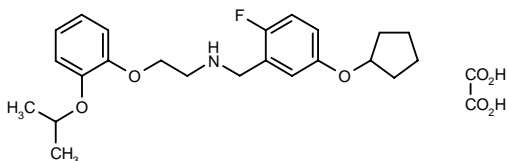
REFERENCES

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2. Gilligan, P.J. et al. *Pyrazolo-[1,5-a]-1,3,5-triazine CRF receptor antagonists: Synthesis and structure-activity relationship of 8-(substituted phenyl) analogs*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 125.
3. He, L. et al. *Pyrazolo-[1,5-a]-1,3,5-triazine CRF receptor antagonists: Synthesis and structure-activity relationships of 8-heteroaryl analogs*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 126.

ANTIPSYCHOTIC DRUGS

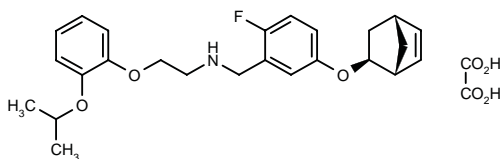
290907

N-[5-(Cyclopentyloxy)-2-fluorobenzyl]-*N*-[2-[2-(isopropoxy)phenoxy]ethyl]amine oxalate



C23 H30 F N O3 . C2 H2 O4; Mol wt: 477.5258

ACTION – Dopamine D2 receptor antagonist for the treatment of psychotic disorders, particularly schizophrenia. The compound gave a pK_i value of 9.13 in *in vitro* studies evaluating affinity for D2 receptors and it proved active in an antidopaminergic test in rats. In a rat model testing for cataleptogenic side effects, this compound exhibited an $ED_{50} > 40$ mg/kg i.p. while risperidone gave an ED_{50} of 4.6 mg/kg. Another exemplified 3-alkoxybenzylamine derivative is:



290908: C25 H30 F N O3 . C2 H2 O4

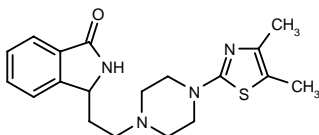
SOURCE – Pierre Fabre.

REFERENCES

1. Vacher, B. et al. (Pierre Fabre Médicament) *Novel 3-alkoxybenzylamine derivs. and their use as medicines for treating schizophrenia*. FR 2786767, WO 0032557.

291611

3-[2-[4-(4,5-Dimethylthiazol-2-yl)piperazin-1-yl]ethyl]-2,3-dihydro-1*H*-isoindol-1-one



C19 H24 N4 O S; Mol wt: 356.4916

ACTION – A specifically claimed compound from a series of 2,3-dihydroisoindol-1-one derivatives that acts as a selective dopamine D4 receptor antagonist ($K_i = 20.8$ nM versus > 5882 nM for D2 receptors in CHO cells) and is thus useful for the treatment of psychosis and schizophrenia, without causing extrapyramidal side effects and tardive dyskinesia.

SOURCE – Pfizer.

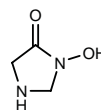
REFERENCES

1. Belliotti, T.R. and Wustrow, D.J. (Warner-Lambert Co.) *Dopamine D4 receptor antagonists*. US 6087364.

S-18841*

255397

3-Hydroxyimidazolidin-4-one



C3 H6 N2 O2; Mol wt: 102.0924

ACTION – Partial agonist at glycine B sites positively coupled to the NMDA receptor, with binding affinity at these sites similar to D-cycloserine ($IC_{50} = 6.8$ and 7.4 μ M, respectively). Like D-cycloserine, compound enhanced the binding of [3 H]-dizocilpine at NMDA receptors ($EC_{50} = 4.3$ and 3 μ M, respectively), and both compounds were similarly effective in inhibiting phencyclidine-induced locomotion in rats ($ID_{50} = 109$ and 107 mg/kg s.c. for compound and D-cycloserine, respectively) and in inducing latent inhibition in rats, a model of cognitive deficit symptoms (minimum effective dose [MED] = 40 mg/kg s.c. for both). At a dose of 40 mg/kg s.c. it did not modify levels of dopamine, noradrenaline or 5-HT in frontal cortex of freely moving rats. Potentially useful as an antipsychotic agent.

SOURCE – ADIR.

REFERENCES

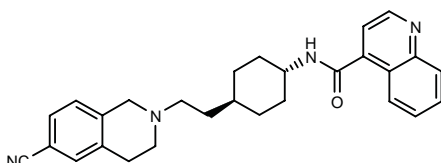
1. Cordi, A. et al. (ADIR et Cie.) *4-Imidazolidinone cpds*. EP 0780379, US 5677325.
2. Cordi, A. et al. *Design, synthesis and structure-activity relationships of novel strychnine-insensitive glycine receptor ligands*. Bioorg Med Chem Lett 1999, 9(10): 1409.
3. Millan, M.J. et al. *S18841, a novel, imidazolinone partial agonist at glycine B receptors of potential utility for the treatment of psychotic disorders*. Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.01.154.

*Identified compound **255397** Drug Data Rep 1998, 020(01): 0027.

SB-277011***271105**

trans-N-[4-[2-(6-Cyano-1,2,3,4-tetrahydro-2-isoquinol-
inyl)ethyl]cyclohexyl]quinoline-4-carboxamide

SB-277011-A



C28 H30 N4 O; Mol wt: 438.5720

Colorless solid, m.p. 207-10 °C.

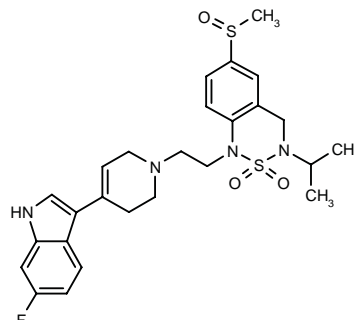
ACTION – Potent and selective dopamine D3 receptor antagonist with high affinity for this receptor ($pK_i = 8.0$) and at least 100-fold selectivity over D2, 5-HT_{1D} and 5-HT_{1B} receptors ($pK_i = 6.0$, 5.9 and < 5.2, respectively), as well as a panel of other receptors and ion channels. Results in a functional assay using CHO cells expressing human D2 and D3 receptors indicated that compound was devoid of agonist-like activity and acted as a potent and selective D3 antagonist ($pK_b = 8.4$ and 6.5 for D3 and D2 antagonism, respectively). Compound displayed an excellent pharmacokinetic profile in rats, with an oral bioavailability of 43% and a half-life of 2 h, with high brain penetration (brain:blood ratio = 3.6:1). It exhibited regional brain selectivity for the nucleus accumbens (in agreement with the regional distribution of D3 receptors), as demonstrated by complete inhibition of dopamine efflux induced by the dopamine agonist quinellorane in the nucleus accumbens but not in the striatum. Compound at doses up to 80 mg/kg p.o. displayed no cataleptogenic activity in rats and did not elevate prolactin levels, in contrast to the typical antipsychotic agent haloperidol. Potential antipsychotic agent with reduced extrapyramidal effects.

SOURCE – SmithKline Beecham.**REFERENCES**

1. Branch, C.L. et al. (SmithKline Beecham plc) *Tetrahydroisoquinoline derivs. as modulators of dopamine D3 receptors*. EP 0983244, WO 9850364.
2. Ashby, C.R. Jr. et al. *Acute and chronic administration of the selective D3 receptor antagonist SB-277011-A alters activity of midbrain dopamine neurons in rats: An in vivo electrophysiological study*. J Pharmacol Exp Ther 2000, 294(3): 1166.
3. McDonald, G. et al. *Novel 2,3,4,5-tetrahydro-1H-3-benzazepines and 2,3-dihydro-1H-isoindoles with high affinity and selectivity for the dopamine D3 receptor*. 27th Natl Med Chem Symp (June 13-17, Kansas City) 2000, Abst B-09.
4. Reavill, C. et al. *Pharmacological actions of a novel, high-affinity, and selective human dopamine D3 receptor antagonist, SB-277011-A*. J Pharmacol Exp Ther 2000, 294(3): 1154.
5. Stemp, G. et al. *Design and synthesis of trans-N-[4-[2-(6-cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-4-quinolinecarboxamide (SB-277011): A potent and selective dopamine D3 receptor antagonist with high oral bioavailability and CNS penetration in the rat*. J Med Chem 2000, 43(9): 1878.

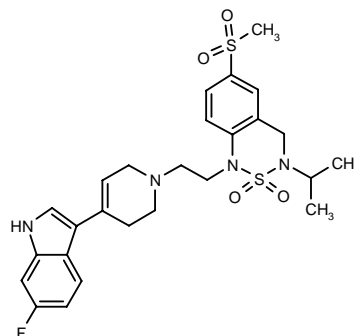
*Identified compound **271105** Drug Data Rep 1999, 021(02): 0114.
**TREATMENT OF MOOD
DISORDERS**
290683

1-[2-[4-(6-Fluoro-1*H*-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-3-isopropyl-6-(methylsulfinyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxide



C26 H31 F N4 O3 S2; Mol wt: 530.6859

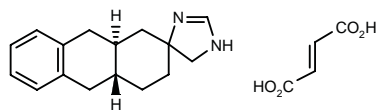
ACTION – Serotonergic modulator that enhances 5-HT release (> 35% increase in [³H]-5-HT release in guinea pig cortical slices at 1 μM), exhibits affinity for 5-HT_{2A} receptors and inhibits 5-HT reuptake. Potentially useful in the treatment of a wide range of conditions such as depression, obesity, bulimia, alcoholism, pain, hypertension, memory loss, sexual dysfunction, anxiety, schizophrenia, epilepsy, gastrointestinal disorders, headache, cardiovascular disorders, smoking cessation, drug addiction, emesis, Alzheimer's disease and sleep disorders. Another specifically claimed compound from this series of indole derivatives is:

**290684:** C26 H31 F N4 O4 S2**SOURCE** – Lilly.**REFERENCES**

1. Fairhurst, J. et al. (Eli Lilly and Company, Ltd.) *Indole derivs. and their use as serotonin receptor ligands*. WO 0031074.

290990

(4a' *R*,9a' *S*)-1',2',3',4,4',5,9',9a',10'-Decahydro-spiro[imidazol-4,2'-anthracene] fumarate



C16 H20 N2 . C4 H4 O4; Mol wt: 356.4196

ACTION – Combined α_2 -adrenoceptor antagonist and monoamine reuptake inhibitor with potential in the treatment of depression, obesity, panic attacks, anxiety, obsessive–compulsive disorders, cognitive disorders, phobia, drug abuse, sexual dysfunction and Parkinson’s disease. In binding assays, compound exhibited pK_i values of 8.0, 6.7 and 7.8 for rat α_2 -adrenoceptors and noradrenaline and 5-HT reuptake sites, respectively. A representative compound from a series of spiroimidazoline derivatives.

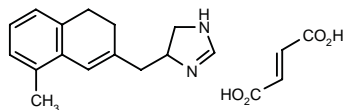
SOURCE – ADIR.

REFERENCES

1. Cordi, A. et al. (ADIR et Cie.) *Spiroimidazoline derivs. and their use as α_2 -adrenergic antagonists and monoamines-reuptake blockers*. EP 1010694, FR 2787450, JP 2000178257.

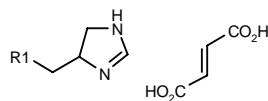
290991

4-(8-Methyl-3,4-dihydronaphthalen-2-ylmethyl)-4,5-dihydro-1 *H*-imidazole fumarate



C15 H18 N2 . C4 H4 O4; Mol wt: 342.3928

ACTION – Combined α_2 -adrenoceptor antagonist and monoamine reuptake inhibitor with potential in the treatment of depression, obesity, panic attacks, anxiety, obsessive–compulsive disorders, cognitive disorders, phobia, drug abuse, sexual dysfunction and Parkinson’s disease. *In vitro*, compound exhibited a pK_i value of 7.8 for rat 5-HT reuptake binding sites. Other exemplified compounds from this series of imidazoline derivatives include the following:



Compound	R1	Formula
290992	3,4-dihydro-2-Naph	C ₁₈ H ₂₀ N ₂ O ₄
290993	2-indanyl	C ₁₇ H ₂₀ N ₂ O ₄

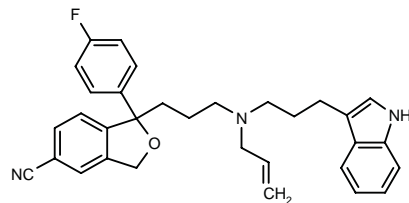
SOURCE – ADIR.

REFERENCES

1. Cordi, A. et al. (ADIR et Cie.) *Imidazoline derivs., preparation and pharmaceutical compsns. containing them*. EP 1010693, FR 2787451, JP 2000178255, US 6127396.

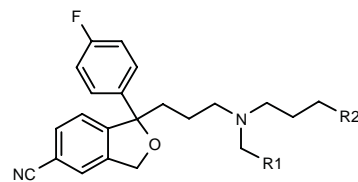
291195

1-[3-[*N*-Allyl-*N*-[3-(1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile



C32 H32 F N3 O; Mol wt: 493.6228

ACTION – Potent 5-HT_{1A} receptor ligand and 5-HT reuptake inhibitor proven to inhibit the binding of the 5-HT_{1A} agonist [³H]-5-carboxamidotryptamine to cloned human receptors by 69% at 100 nM and the accumulation of tritiated 5-HT into whole brain synaptosomes by 73% at the same concentration. Potentially useful for the treatment of certain psychiatric and neurological disorders and particularly preferred for the therapy of depression. Other exemplified benzofuran derivatives include the following:



Compound	R1	R2	Formula
291197	vinyl	3-MeO-Ph	C ₃₁ H ₃₃ FN ₂ O ₂
291199	H	2-MeO-PhO	C ₂₉ H ₃₁ FN ₂ O ₃
291200	vinyl	2-MeO-PhO	C ₃₁ H ₃₃ FN ₂ O ₃

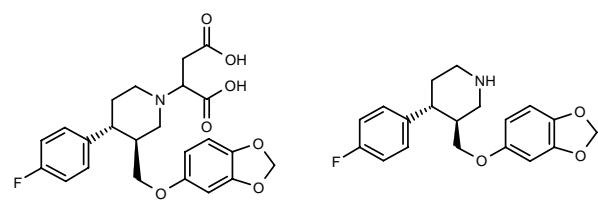
SOURCE – Lundbeck.

REFERENCES

1. Andersen, K. et al. (H. Lundbeck A/S) *Benzofuran derivs., their preparation and use*. WO 0034263.

291499

2-[3(*S*)-(Benzodioxol-5-yloxymethyl)-4(*R*)-(4-fluoro-phenyl)-1-piperidinyl]succinic acid paroxetine salt



C23 H24 F N O7 . C19 H20 F N O3; Mol wt: 774.8096

ACTION – Paroxetine derivative with potential for the treatment or prevention of CNS disorders, particularly depression, obsessive–compulsive disorder and panic.

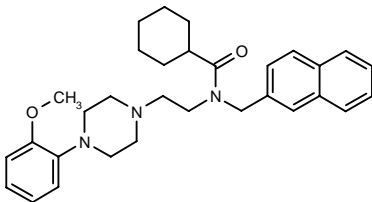
SOURCE – SmithKline Beecham.

REFERENCES

1. Jones, D.A. (SmithKline Beecham plc) *Deriv. of paroxetine*. WO 0035910.

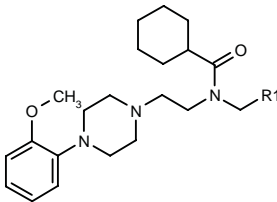
291559

N-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-N-(2-naphthalenylmethyl)cyclohexanecarboxamide



C31 H39 N3 O2; Mol wt: 485.6681

ACTION – Agent with high binding affinity for 5-HT_{1A} receptors and therefore considered useful for the treatment of depression, anxiety, panic, sleep disorders, sexual dysfunction, drug or alcohol addiction, cognitive disorders, neurodegenerative diseases, migraine and obesity. It was found to displace [³H]-8-OH-DPAT binding in CHO cells with a K_i value of 1.2 nM. Other specifically claimed piperazine ethylamide derivatives are:



Compound	R1	Formula
291560	Ph	C ₂₇ H ₃₇ N ₃ O ₂
291561	1-Naph	C ₃₁ H ₃₉ N ₃ O ₂
291562	CH2CH2Ph	C ₂₉ H ₄₁ N ₃ O ₂

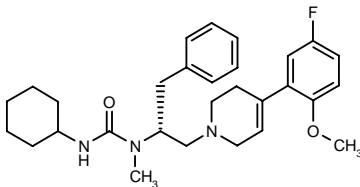
SOURCE – American Home Products.

REFERENCES

1. Kelly, M.G. and Palmer, Y.L. (American Home Products Corp.) *Piperazine ethylamide derivs. with 5-HT_{1A} receptor activity*. WO 0035892.

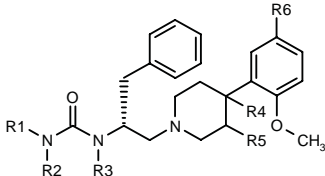
291563

N-[1(R)-Benzyl-2-[4-(5-fluoro-2-methoxyphenyl)-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-N'-cyclohexyl-N-methylurea



C29 H38 F N3 O2; Mol wt: 479.6362

ACTION – Compound with 5-HT_{1A} receptor binding affinity, as demonstrated by its ability to displace [³H]-8-OH-DPAT binding in CHO cells (K_i = 3.5 nM) and reverse cAMP stimulation in CHO cells transfected with the human 5-HT_{1A} receptor (IC₅₀ = 0.29 nM). Potentially useful for the treatment of depression, anxiety, panic, sleep disorders, sexual dysfunction, drug or alcohol addiction, cognitive disorders, neurodegenerative diseases, migraine and obesity. Other specifically claimed arylpiperidine and aryl-1,2,5,6-tetrahydropyridne urea derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Formula
291564	H	cyclohexyl	Me	H	H	F	C ₂₉ H ₄₀ FN ₃ O ₂
291565	-CH2CH2OCH2CH2-		Me	bond		F	C ₂₇ H ₃₄ FN ₃ O ₃
291566	H	cyclohexyl	H	H	H	H	C ₂₈ H ₃₉ N ₃ O ₂

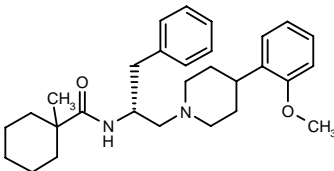
SOURCE – American Home Products.

REFERENCES

1. Kelly, M.G. and Zhang, G. (American Home Products Corp.) *Arylpiperidine and aryl-1,2,5,6-tetrahydropyridine urea derivs. having 5HT_{1A} receptor activity*. WO 0035875.

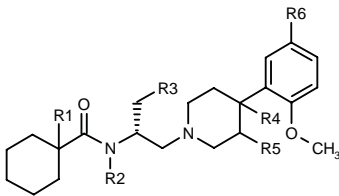
291567¹

N-[1(R)-Benzyl-2-[4-(2-methoxyphenyl)piperidin-1-yl]ethyl]-1-methylcyclohexanecarboxamide



C29 H40 N2 O2; Mol wt: 448.6470

ACTION – Compound with 5-HT_{1A} receptor binding affinity, as demonstrated by its ability to displace [³H]-8-OH-DPAT binding in CHO cells (K_i = 0.24 nM) and reverse cAMP stimulation in CHO cells transfected with the human 5-HT_{1A} receptor (IC₅₀ = 0.29 nM). Potentially useful for the treatment of depression, anxiety, panic, sleep disorders, sexual dysfunction, drug or alcohol addiction, cognitive disorders, neurodegenerative diseases, migraine and obesity. Other specifically claimed arylpiperidine and aryl-1,2,5,6-tetrahydropyridne amide derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Formula
291568 ^{1,2}	Me	Me	Ph	H	H	F	C ₃₀ H ₄₁ FN ₂ O ₂
291569 ^{1,2}	Me	Me	Ph	bond		F	C ₃₀ H ₃₉ FN ₂ O ₂
291570 ¹	H	H	Ph	bond		H	C ₂₈ H ₃₈ N ₂ O ₂
291571 ^{1,2}	Me	H	Ph	bond		H	C ₂₉ H ₃₈ N ₂ O ₂
291572 ¹	H	H	Ph	H	H	H	C ₂₈ H ₃₈ N ₂ O ₂
291573 ¹	Me	H	3-Pyr	H	H	H	C ₂₈ H ₃₉ N ₃ O ₂
291574 ¹	Me	H	4-Pyr	H	H	H	C ₂₈ H ₃₉ N ₃ O ₂
291575 ¹	H	Me	3-Pyr	H	H	H	C ₂₈ H ₃₉ N ₃ O ₂
291576 ¹	H	Me	4-Pyr	H	H	H	C ₂₈ H ₃₉ N ₃ O ₂
291577 ¹	H	H	4-MeO-Ph	H	H	H	C ₂₉ H ₄₀ N ₂ O ₃

SOURCE – American Home Products.

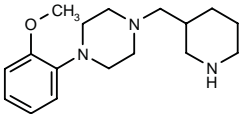
REFERENCES

1. Kelly, M.G. et al. (American Home Products Corp.) *Arylpiperidine and aryl-1,2,5,6-tetrahydropyridine amide derivs. having 5HT_{1A} receptor activity.* WO 0035874.

2. Zhang, G. et al. *Design and synthesis of potent and selective 5-HT_{1A} receptor ligands.* 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 119.

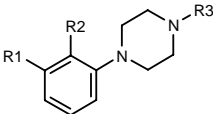
291578

1-(2-Methoxyphenyl)-4-(3-piperidinylmethyl)piperazine



C17 H27 N3 O; Mol wt: 289.4203

ACTION – Agent with high binding affinity for 5-HT_{1A} receptors and thus potentially useful for the treatment of depression, anxiety, panic, sleep disorders, sexual dysfunction, drug or alcohol addiction, cognitive disorders, neurodegenerative diseases, migraine and obesity. It was found to displace [³H]-8-OH-DPAT binding in CHO cells, giving a K_i value of 2.0 nM. Other specifically claimed piperazine derivatives are:



Compound	R1	R2	R3	Formula
291579	H	OMe	4-Pip-CH2	C ₁₇ H ₂₇ N ₃ O
291580	H	OMe	1-(cyclohexyl-CO)-4-Pip-CH2	C ₂₄ H ₃₇ N ₃ O ₂
291581	H	OMe	1-(cyclohexyl-CH2)-3-Pip-CH2	C ₂₄ H ₃₉ N ₃ O
291582	H	OMe	1-(PhCO)-4-Pip-CH2	C ₂₄ H ₃₁ N ₃ O ₂
291583	H	OMe	1-(PhCH2)-4-Pip-CH2	C ₂₄ H ₃₃ N ₃ O
291584	H	OMe	1-(cyclohexyl-CO)-3-Pip-CH2	C ₂₄ H ₃₇ N ₃ O ₂
291585	H	OMe	1-(PhCO)-3-Pip-CH2	C ₂₄ H ₃₁ N ₃ O ₂
291586	H	OMe	1-(PhCH2)-3-Pip-CH2	C ₂₄ H ₃₃ N ₃ O

Compound	R1	R2	R3	Formula
291587	H	OMe	1-(3-indolylCH2CH2)-3-Pip-CH2	C ₂₇ H ₃₈ N ₄ O
291588	-NHCH=CH-		4-Pip-CO	C ₁₈ H ₂₄ N ₄ O
291589	-NHCH=CH-		1-Me-4-Pip-CH2	C ₁₉ H ₂₈ N ₄

SOURCE – American Home Products.

REFERENCES

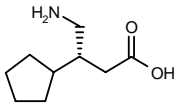
1. Kelly, M.G. and Palmer, Y.L. (American Home Products Corp.) *1,4-Piperazine derivs. having 5HT_{1A} receptor activity.* WO 0035878.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

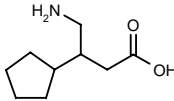
290681^{1,2}

(+)-4-Amino-3(*R*)-cyclopentylbutyric acid



C9 H17 N O2; Mol wt: 171.2383

ACTION – Agent for the treatment of epilepsy and other neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal damage and inflammation with good binding affinity for the Ca²⁺ channel α2-δ subunit (IC₅₀ = 0.108 μM vs. IC₅₀ = 0.10-0.12 μM for gabapentin) and thus expected to have similar pharmacological effects to gabapentin. When tested *in vivo*, orally administered compound was active in an audiogenic seizure model in DBA/2 mice, as well as in the cargeenan-induced hyperalgesia model and the Vogel conflict test in rats. Another specifically claimed compound from this series of γ-aminobutyric acid analogues is:



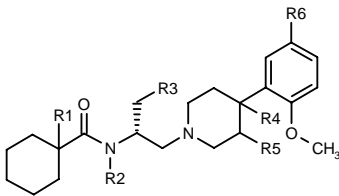
290682¹: C9 H17 N O2

SOURCE – Pfizer.

REFERENCES

1. Belliotti, T.R. and Wustrow, D.J. (Pfizer Inc.) *Improved γ amino butyric acid analogs.* WO 0031020.

2. Belliotti, T. et al. *3-Cycloalkyl-substituted GABA compounds as gabapentin analogs.* 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 245.



Compound	R1	R2	R3	R4	R5	R6	Formula
291568 ^{1,2}	Me	Me	Ph	H	H	F	C ₃₀ H ₄₁ FN ₂ O ₂
291569 ^{1,2}	Me	Me	Ph	bond		F	C ₃₀ H ₃₉ FN ₂ O ₂
291570 ¹	H	H	Ph	bond		H	C ₂₈ H ₃₈ N ₂ O ₂
291571 ^{1,2}	Me	H	Ph	bond		H	C ₂₉ H ₃₈ N ₂ O ₂
291572 ¹	H	H	Ph	H	H	H	C ₂₈ H ₃₈ N ₂ O ₂
291573 ¹	Me	H	3-Pyr	H	H	H	C ₂₈ H ₃₉ N ₃ O ₂
291574 ¹	Me	H	4-Pyr	H	H	H	C ₂₈ H ₃₉ N ₃ O ₂
291575 ¹	H	Me	3-Pyr	H	H	H	C ₂₈ H ₃₉ N ₃ O ₂
291576 ¹	H	Me	4-Pyr	H	H	H	C ₂₈ H ₃₉ N ₃ O ₂
291577 ¹	H	H	4-MeO-Ph	H	H	H	C ₂₉ H ₄₀ N ₂ O ₃

SOURCE – American Home Products.

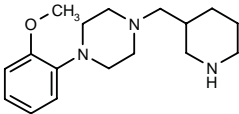
REFERENCES

1. Kelly, M.G. et al. (American Home Products Corp.) *Arylpiperidine and aryl-1,2,5,6-tetrahydropyridine amide derivs. having 5HT_{1A} receptor activity.* WO 0035874.

2. Zhang, G. et al. *Design and synthesis of potent and selective 5-HT_{1A} receptor ligands.* 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 119.

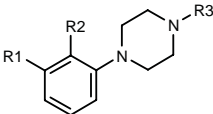
291578

1-(2-Methoxyphenyl)-4-(3-piperidinylmethyl)piperazine



C17 H27 N3 O; Mol wt: 289.4203

ACTION – Agent with high binding affinity for 5-HT_{1A} receptors and thus potentially useful for the treatment of depression, anxiety, panic, sleep disorders, sexual dysfunction, drug or alcohol addiction, cognitive disorders, neurodegenerative diseases, migraine and obesity. It was found to displace [³H]-8-OH-DPAT binding in CHO cells, giving a K_i value of 2.0 nM. Other specifically claimed piperazine derivatives are:



Compound	R1	R2	R3	Formula
291579	H	OMe	4-Pip-CH2	C ₁₇ H ₂₇ N ₃ O
291580	H	OMe	1-(cyclohexyl-CO)-4-Pip-CH2	C ₂₄ H ₃₇ N ₃ O ₂
291581	H	OMe	1-(cyclohexyl-CH2)-3-Pip-CH2	C ₂₄ H ₃₉ N ₃ O
291582	H	OMe	1-(PhCO)-4-Pip-CH2	C ₂₄ H ₃₁ N ₃ O ₂
291583	H	OMe	1-(PhCH2)-4-Pip-CH2	C ₂₄ H ₃₃ N ₃ O
291584	H	OMe	1-(cyclohexyl-CO)-3-Pip-CH2	C ₂₄ H ₃₇ N ₃ O ₂
291585	H	OMe	1-(PhCO)-3-Pip-CH2	C ₂₄ H ₃₁ N ₃ O ₂
291586	H	OMe	1-(PhCH2)-3-Pip-CH2	C ₂₄ H ₃₃ N ₃ O

Compound	R1	R2	R3	Formula
291587	H	OMe	1-(3-indolylCH2CH2)-3-Pip-CH2	C ₂₇ H ₃₈ N ₄ O
291588	-NHCH=CH-		4-Pip-CO	C ₁₈ H ₂₄ N ₄ O
291589	-NHCH=CH-		1-Me-4-Pip-CH2	C ₁₉ H ₂₈ N ₄

SOURCE – American Home Products.

REFERENCES

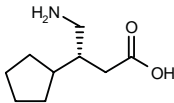
1. Kelly, M.G. and Palmer, Y.L. (American Home Products Corp.) *1,4-Piperazine derivs. having 5HT_{1A} receptor activity.* WO 0035878.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

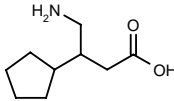
290681^{1,2}

(+)-4-Amino-3(*R*)-cyclopentylbutyric acid



C9 H17 N O2; Mol wt: 171.2383

ACTION – Agent for the treatment of epilepsy and other neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal damage and inflammation with good binding affinity for the Ca²⁺ channel α2-δ subunit (IC₅₀ = 0.108 μM vs. IC₅₀ = 0.10-0.12 μM for gabapentin) and thus expected to have similar pharmacological effects to gabapentin. When tested *in vivo*, orally administered compound was active in an audiogenic seizure model in DBA/2 mice, as well as in the cargeenan-induced hyperalgesia model and the Vogel conflict test in rats. Another specifically claimed compound from this series of γ-aminobutyric acid analogues is:



290682¹: C9 H17 N O2

SOURCE – Pfizer.

REFERENCES

1. Belliotti, T.R. and Wustrow, D.J. (Pfizer Inc.) *Improved γ amino butyric acid analogs.* WO 0031020.

2. Belliotti, T. et al. *3-Cycloalkyl-substituted GABA compounds as gabapentin analogs.* 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 245.

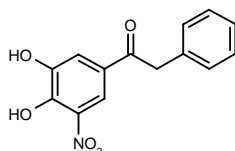
TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

BIA-3-202

291041

1-(3,4-Dihydroxy-5-nitrophenyl)-2-phenyl-1-ethanone

BIA-3-02



C14 H11 N O5; Mol wt: 273.2429

ACTION – An inhibitor of catechol-*O*-methyltransferase (COMT; $IC_{50} = 3.7$ and 696 nM, respectively, against rat brain and liver enzyme) with potential for the treatment of central and peripheral nervous system disorders such as Parkinson's disease and parkinsonian disorders, as well as gastrointestinal disturbances, edema formation and hypertension. When tested *in vivo* in rats, compound was shown to preferentially inhibit liver over brain COMT following intragastric administration ($ED_{50} = 0.7 \pm 0.1$ mg/kg and 5.3 ± 1.1 mg/kg, respectively), with a duration of action over 9 h. A representative compound from a series of substituted 2-phenyl-1-(3,4-dihydroxy-5-nitrophenyl)-1-ethanones.

SOURCES – Bial; Portela.

REFERENCES

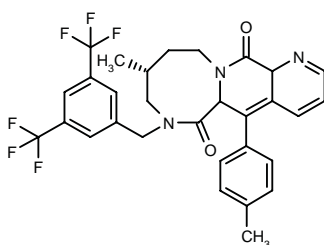
1. Benes, J. et al. (Portela & Ca., SA) *Substd. 2-phenyl-1-(3,4-dihydroxy-5-nitrophenyl)-1-ethanones, their use in the treatment of some central and peripheral nervous system disorders and pharmaceutical compsns. containing them.* EP 1010688, GB 2344819, WO 0037423.

2. Learmonth, D. et al. *Synthesis of 1-(3,4-dihydroxy-5-nitrophenyl)-2-phenyl-ethanone and derivatives as potent and selective inhibitors of catechol-*O*-methyltransferase (COMT).* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-34.

TREATMENT OF NAUSEA AND VOMITING

291126

7-[3,5-Bis(trifluoromethyl)benzyl]-9(*R*)-methyl-5-(4-methylphenyl)-6,7,8,9,10,11,13,13a-octahydro-5a*H*-[1,4]diazocino[2,1-*g*][1,7]naphthyridine-6,13-dione



C30 H27 F6 N3 O2; Mol wt: 575.5503

ACTION – Antiemetic agent proven active in several animal models of cisplatin-, methotrexate-, morphine-, loperamide- and apomorphine-induced emesis.

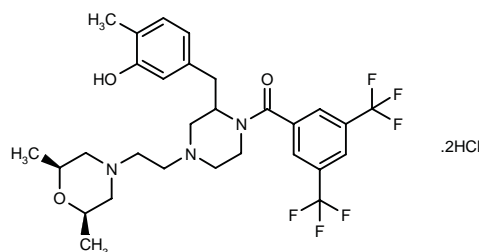
SOURCE – Takeda.

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1. Doi, T. et al. (Takeda Chemical Industries, Ltd.) *Drugs.* WO 0032192.

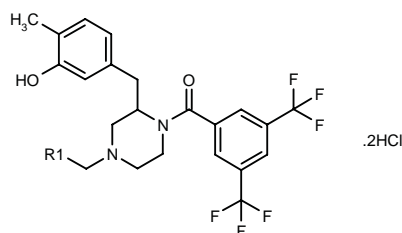
291510

cis-1-[3,5-Bis(trifluoromethyl)phenyl]-1-[4-[2-(2,6-dimethylmorpholin-4-yl)ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazin-1-yl]methanone dihydrochloride



C29 H35 F6 N3 O3 . 2HCl; Mol wt: 660.5233

ACTION – Tachykinin antagonist with potential for the treatment of tachykinin-mediated diseases including respiratory diseases such as asthma, bronchitis, rhinitis and cough, ophthalmic diseases such as conjunctivitis, skin diseases such as contact dermatitis, atopic dermatitis and urticaria, inflammatory diseases such as rheumatoid arthritis and osteoarthritis, and pain. Compound was shown to potently bind to human NK_1 receptors expressed in CHO cells and produced 100% inhibition of apomorphine-induced emesis in dogs at 0.32 mg/kg i.v. Other compounds from this series of piperazine derivatives include the following:



Compound	R1	Formula
291511	5(S)-Me-2(S)-(MeOCH2)-4-morpholinyl-CH2	C ₃₀ H ₃₇ F ₆ N ₃ O ₄ ·2HCl
291512	3-Pyr-ethynylene	C ₂₈ H ₂₅ F ₆ N ₃ O ₂ ·2HCl
291513	3-Pyr-CH2CH2	C ₂₉ H ₂₉ F ₆ N ₃ O ₂ ·2HCl

SOURCE – Fujisawa.

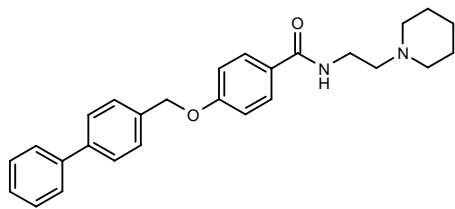
REFERENCES

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COGNITION-ENHANCING DRUGS

290728

4-(Biphenyl-4-ylmethoxy)-N-[2-(1-piperidinyl)ethyl]-benzamide



C27 H30 N2 O2; Mol wt: 414.5460

ACTION – β -Amyloid (A β) protein production inhibitor shown to inhibit the formation of proteins A β 1-40 and A β 1-42 in human neuroblastoma IMR-32 cells. Potentially useful for the treatment of neurological disorders related to A β production, i.e., Alzheimer's disease, Parkinson's disease or Down's syndrome.

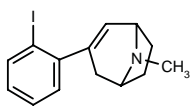
SOURCE – Takeda.

REFERENCES

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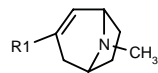
290946

(\pm)-3-(2-Iodophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene

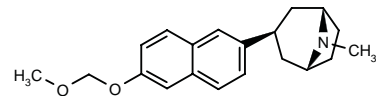


C14 H16 I N; Mol wt: 325.1874

ACTION – Nicotinic acetylcholine receptor (AChR) modulator with potential in the treatment of conditions involving the cholinergic system of the CNS including Alzheimer's disease and other cognitive and neuro-degenerative disorders, disorders associated with smooth muscle contraction, endocrine disorders, pain, inflammatory disorders and withdrawal from tobacco and other addictive substances. Other specifically claimed compounds from this series of 8-azabicyclo[3.2.1]oct-2-ene and -octane derivatives include the following:



Compound	R1	Formula
290947	2-Br-Ph	C ₁₄ H ₁₆ BrN
290949	6-SH-2-Naph	C ₁₈ H ₁₉ NS
290950	6-N(Me)2-2-Naph	C ₂₀ H ₂₄ N ₂
290951	6-(perhydro-1,4-diazepin-1-yl)-2-Naph	C ₂₃ H ₂₉ N ₃
290952	6-I-2-Naph	C ₁₈ H ₁₈ IN
290953	7-I-2-Naph	C ₁₈ H ₁₈ IN



290948: C20 H25 N O2

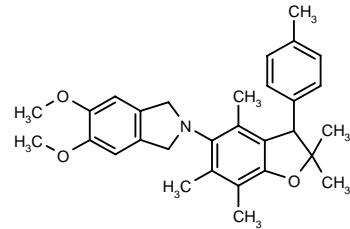
SOURCE – NeuroSearch.

REFERENCES

1. Peters, D. et al. (NeuroSearch A/S) *8-Azabicyclo[3.2.1]oct-2-ene and -octane derivs.* WO 0032600.

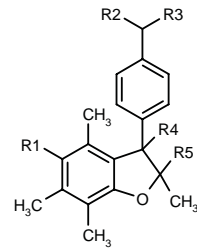
291066

5,6-Dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran-5-yl]isoindoline



C30 H35 N O3; Mol wt: 457.6105

ACTION – Neuroprotective agent that acts by inhibiting nerve degeneration. It was active in inhibiting LY-294002-induced nerve cell degeneration using human neuroblastoma SK-N-SH cells, exhibiting 28.2% protection. Potentially useful for the treatment of Alzheimer's disease and Parkinson's disease. Other exemplified benzofuran derivatives include the following:



Compound	R1	R2=R3	R4	R5	Formula
291068	6H-1,3-dioxolo-[4,5-f]isoindol-6-yl	H	H	Me	C ₂₉ H ₂₉ NO ₃
291069	4-F-PhCH ₂ NH	Me	H	Me	C ₂₉ H ₃₄ FNO
291071	4-MeO-PhCH ₂ NH	Me	bond		C ₂₉ H ₃₃ NO ₂

SOURCE – Takeda.

REFERENCES

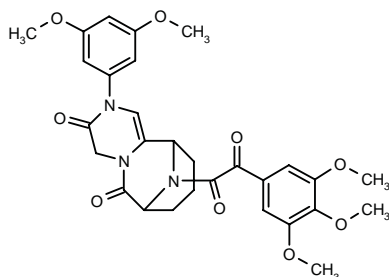
1. Ohkawa, S. et al. (Takeda Chemical Industries, Ltd.) *Benzofuran derivs., process for the preparation of the same and uses thereof*. JP 2000226388, WO 0034262.

AG-5507*

285600

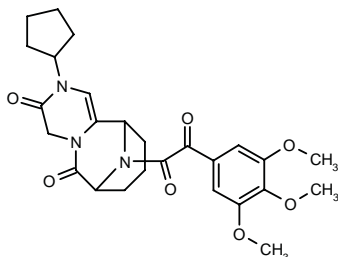
4-(3,5-Dimethoxyphenyl)-13-[2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl]-4,7,13-triazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-5,8-dione

2-(3,5-Dimethoxyphenyl)-12-[2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl]-8,9,10,11-tetrahydro-7,11-imino-2*H*-pyrazino[1,2-*a*]azocine-3,6(4*H*,7*H*)-dione



C29 H31 N3 O9; Mol wt: 565.5759

ACTION – Neurotrophic agent that acts by inhibiting rotamase (peptidylprolyl isomerase) activity associated with the FK-506-binding protein FKBP-12 ($K_i = 54$ nM). Potentially useful for promoting the repair of neuronal damage caused by disease or physical trauma, e.g., Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. Another polycyclic azamide is:



AG-5473 [285599]**: C26 H31 N3 O7

SOURCE – Agouron (Pfizer).

REFERENCES

1. Kato, S. et al. (Agouron Pharmaceuticals, Inc.) *Cpds., compsns., and methods for stimulating neuronal growth and elongation*. WO 0004020.
2. Guo, C. et al. *Concise synthesis of AG5473/5507 utilizing N-acyliminium ion chemistry*. 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst ORGN 453.
3. Guo, C.X. et al. *A concise synthesis of AG5473/5507 utilizing N-acyliminium ion chemistry*. Tetrahedron Lett 2000, 41(28): 5307.

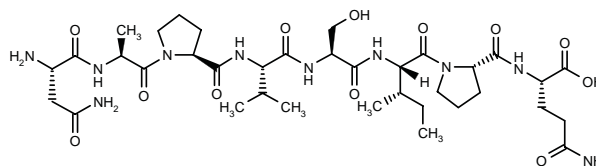
*Identified compound **285600** (see **285593**) Drug Data Rep 2000, 022(05): 0411.

Identified compound **285599 (see **285593**) Drug Data Rep 2000, 022(05): 0411.

NAP

291120

L-Asparaginyl-L-alanyl-L-prolyl-L-valyl-L-seryl-L-isoleucyl-L-prolyl-L-glutamine



C36 H60 N10 O12; Mol wt: 824.9280

ACTION – Neuroprotective peptide fragment derived from activity-dependent neuroprotective protein (ADPN), with *in vitro* protective activity against oxidative insult in neuronal systems. Compound also induced an increase in cGMP and nitric oxide production *in vitro*. Furthermore, it was able to cross the blood-brain barrier when given intranasally and induced a marked improvement in spatial memory in a water maze test in rats when administered by this route. Potentially useful for the treatment of Alzheimer's disease.

SOURCES – National Institutes of Health, Bethesda, MD (US); Tel Aviv University, Tel Aviv (IL).

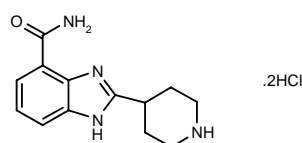
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1. Gozes, I. et al. (US Department of Health & Human Services) *Activity dependent neurotrophic factor III (ADNF III)*. WO 9835042.
2. Gozes, I. et al. (US Department of Health & Human Services; Ramot - University Authority for Applied Research & Industrial Development Ltd.) *Activity dependent neurotrophic factor III (ADNF III)*. WO 0027875.
3. Bassan, M. et al. *Complete sequence of a novel protein containing a femtomolar-activity-dependent neuroprotective peptide*. J Neurochem 2000, 72(3): 1283.
4. Gozes, I. et al. *A novel approach to Alzheimer's disease treatment: Intranasal application of neuroprotective peptide fragments*. Neurobiol Aging 2000, 21(15): Abst 767.
5. Sherki, O.D. et al. *Vasoactive intestinal peptide (VIP) prevents neurotoxicity in neuronal cultures: Relevance to neuroprotection in Parkinson's disease*. Brain Res 2000, 854(1-2): 257.

TREATMENT OF CEREBROVASCULAR DISEASES

290906

2-(4-Piperidiny)-1*H*-benzimidazole-4-carboxamide dihydrochloride



C13 H16 N4 O . 2HCl; Mol wt: 317.2182

ACTION – PARP (poly[ADP-ribose] polymerase or NAD+ ADP-ribosyltransferase) inhibitor, potentially useful for the treatment of neurological and neurodegenerative disorders including cerebral ischemia, traumatic brain injury, Alzheimer's disease, Huntington's disease, Parkinson's disease, etc., with improved solubility in water (0.5%).

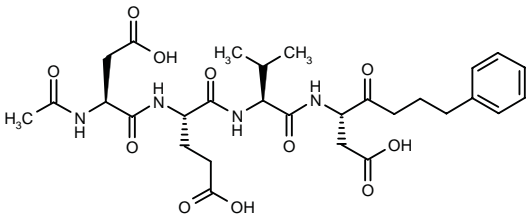
SOURCE – BASF.

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1. Lubisch, W. et al. (BASF AG) *Substd. benzimidazoles and their use as PARP inhibitors*. WO 0032579.

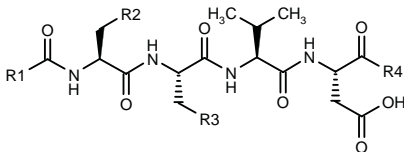
290976

3(S)-(N-Acetyl-L-aspartyl-L-glutamyl-L-valylamino)-4-oxo-7-phenylheptanoic acid



C29 H40 N4 O11; Mol wt: 620.6520

ACTION – Caspase 3 inhibitor with potential in the treatment of caspase 3-mediated conditions, particularly cardiac and cerebral ischemia/reperfusion injury (e.g., stroke), type 1 diabetes, AIDS, cerebral and spinal cord trauma, organ damage during transplantation, alopecia, aging, Parkinson's disease, Alzheimer's disease, Down's syndrome, spinal muscular atrophy and multiple sclerosis. Other specifically claimed compounds from this series of γ -ketoacid tetrapeptides include the following:



Compound	R1	R2	R3	R4	Formula
290977	Me	CO2H	CH2-CO2H	Pr	C ₂₃ H ₃₆ N ₄ O ₁₁
290978	Me	CO2H	CH2-CO2H	4-MeO-Ph(CH2)3	C ₃₀ H ₄₂ N ₄ O ₁₂
290979	Me	CO2H	CH2-CO2H	4-Me-2-oxo-2H-1-benzopyran-7-yl-NH	C ₃₀ H ₃₇ N ₅ O ₁₃
290980	3,5-(Br)2-Ph	CO2H	H	(CH2)3Ph	C ₃₂ H ₃₈ Br ₂ N ₄ O ₉
290981	Me	CO2H	H	1-Naph-(CH2)3	C ₃₁ H ₄₀ N ₄ O ₉
290982	Me	CO2H	CH2-SO2Me	(CH2)3Ph	C ₂₉ H ₄₂ N ₄ O ₁₁ S
290983	Me	SMe	H	1-Naph-(CH2)3	C ₃₁ H ₄₂ N ₄ O ₇ S
290985	Me	CO2Me	H	(CH2)3Ph	C ₂₈ H ₄₀ N ₄ O ₉

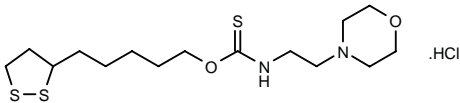
SOURCE – Merck & Co.

REFERENCES

1. Grimm, E.L. et al. (Merck Frosst Canada Inc.) *γ -Ketoacid tetrapeptides as inhibitors of caspase-3*. WO 0032620.

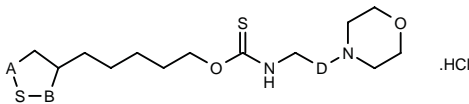
291027

2-(4-Morpholinyl)ethylcarbamothioic acid O-[5-(1,2-dithiolan-3-yl)pentyl] ester hydrochloride



C15 H28 N2 O2 S3 . HCl; Mol wt: 401.0571

ACTION – Antioxidant with potential for the treatment of cerebral ischemia, epilepsy, neurodegenerative disorders such as Alzheimer's disease and Pick's disease. *In vitro*, compound was shown to protect against against L-homo-cysteinic acid-induced toxicity in murine hippocampal HT-22 cells (PC₅₀ = 15.5 μ M) and produced 90% inhibition of FeSO₄/ascorbic acid/H₂O₂-induced lipid peroxidation in murine cortical membranes at a concentration of 5 mM. *In vivo*, it provided 100% protection against *tert*-butylhydroperoxide-induced lethality in mice at a dose of 150 mg/kg i.p. and produced 100 and 92% inhibition of alloxan-induced hyperglycemia in mice when given at 400 mg/kg p.o. 1 or 3 h, respectively, prior to alloxan injection. Other specifically claimed compounds from this series of 1,2-dithiolane derivatives include the following:



Compound	A	B	D	Isomer	Formula
291028	CH2	S	-CH2-	S	C ₁₅ H ₂₈ N ₂ O ₂ S ₃ .HCl
291029	CH2	S	-CH2-	R	C ₁₅ H ₂₈ N ₂ O ₂ S ₃ .HCl
291030	CH2	S	-(CH2)2-		C ₁₆ H ₃₀ N ₂ O ₂ S ₃ .HCl
291031	S	CH2	-CH2-		C ₁₅ H ₂₈ N ₂ O ₂ S ₃ .HCl

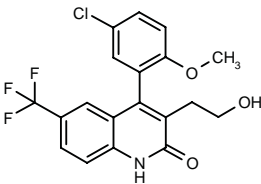
SOURCE – ADIR.

REFERENCES

1. Golstein, S. et al. (ADIR et Cie.) *1,2-Dithiolane derivs., their process of preparation and pharmaceutical compsns. containing them*. EP 1010698, FR 2787109, JP 2000178270.

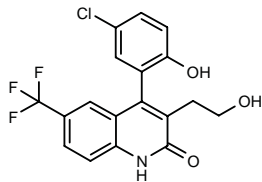
291065

4-(5-Chloro-2-methoxyphenyl)-3-(2-hydroxyethyl)-6-(trifluoromethyl)quinolin-2(1H)-one



C19 H15 Cl F3 N O3; Mol wt: 397.7785

ACTION – Modulator of the large-conductance calcium-activated potassium (BK_{Ca}) channel, able to open BK_{Ca} channels and increase whole-cell outward (K⁺) BK_{Ca}-mediated currents in *Xenopus* oocytes under voltage-clamp conditions, exhibiting a > 200% increase over controls. It was also active in reducing cell loss resulting from neuronal ischemia in a middle cerebral artery occlusion (MCAO) model in spontaneously hypertensive rats, reducing cortical infarct volume by about 25% when administered at 0.003 mg/kg as a single bolus 2 h after MCAO as compared to vehicle-treated controls. This compound is expected to be useful for the treatment of ischemia, stroke, epilepsy, convulsions, asthma, irritable bowel syndrome, migraine, traumatic brain injury, spinal cord injury, sexual dysfunction and urinary incontinence. Another specifically claimed compound form this series of 3-substituted-4-arylquinolin-2-one derivatives is:



291067: C18 H13 Cl F3 N O3

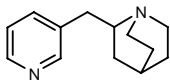
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Hewawasam, P. and Starrett, J.E. Jr. (Bristol-Myers Squibb Co.) *3-Substd.-4-arylquinolin-2-one derivs. as potassium channel modulators*. WO 0034244.

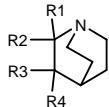
291318

2-(3-Pyridinylmethyl)quinuclidine



C13 H18 N2; Mol wt: 202.2992

ACTION – Nicotinic acetylcholine receptor antagonist with selectivity for the $\alpha 4\beta 2$ receptor subtype versus the $\alpha 7$ subtype (K_i = 37 nM and 50 μ M, respectively). Potentially useful as a neuroprotectant, anticonvulsant and antidepressant, among others. Other exemplified compounds from this series of pyridyl-bridgehead derivatives are:



Compound	R1	R2	R3	R4	Formula
291319	3-Pyr-CH2	H	-O-		C ₁₃ H ₁₆ N ₂ O
291320	-CH(3-Pyr)-		H	H	C ₁₃ H ₁₆ N ₂
291321	3-Pyr-CH2	H	OH	H	C ₁₃ H ₁₈ N ₂ O
291322	3-THF-CH2	H	-O-		C ₁₂ H ₁₉ NO ₂

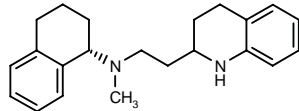
SOURCE – R.J. Reynolds Tobacco.

REFERENCES

1. Schmitt, J.D. et al. (R.J. Reynolds Tobacco Co.) *Pyridyl-bridgehead derivs. and their analogues, pharmaceutical compsns. and their use as inhibitors of nicotinic cholinergic receptors*. WO 0034276.

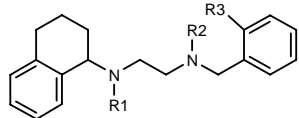
291594

N-Methyl-*N*-[1,2,3,4-tetrahydronaphthalen-1(*S*)-yl]-*N*-[2-(1,2,3,4-tetrahydroquinolin-2-yl)ethyl]amine



C22 H28 N2; Mol wt: 320.4772

ACTION – Agent for the treatment of neurological disorders found to selectively bind at the [³H]-emopamil binding site (IC₅₀ = 14 nM for the [³H]-emopamil binding site versus 7590 nM for the [³H]-D-888 binding site). The compound was active in a global model of cerebral ischemia in gerbils and in transient or permanent focal ischemia in rats. Particularly useful for the treatment of stroke, head trauma, transient cerebral ischemic attacks, Alzheimer’s disease, Parkinson’s disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis and AIDS-related dementia. Other exemplified 1,2,3,4-tetrahydronaphthalenes include the following:



Compound	R1	R2	R3	Isomer	Formula
291595	H	Me	H	S	C ₂₀ H ₂₆ N ₂
291596	Me	-(CH2)2-		R	C ₂₂ H ₂₈ N ₂

SOURCE – AstraZeneca.

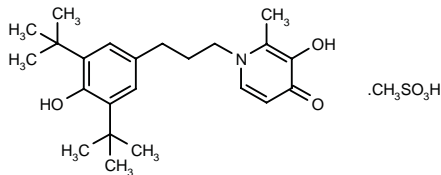
REFERENCES

1. Chen, D.W.C. and Forst, J.M. (AstraZeneca UK, Ltd.) *1,2,3,4-Tetrahydronaphthalenes and their pharmaceutical use*. WO 0035882.

CEB-1370*

276705

1-[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)propyl]-3-hydroxy-2-methylpyridin-4(1*H*)-one methanesulfonate



C23 H33 N O3 . C H4 O3 S; Mol wt: 467.6233

ACTION – Neuroprotective agent with potent inhibitory activity against lipid peroxidation in rat brain homogenates ($IC_{50} = 1.0 \mu M$) and the ability to protect cerebellar granule cells from iodoacetate (IAA)-induced toxicity ($EC_{50} = 0.3 \mu M$), being more potent than deferiprone, BHT, trolox and LY-231617 ($EC_{50} = 46.7, 6.0, 77.8$ and $5.0 \mu M$, respectively). Compound also inhibited oxidative stress resulting from neural toxicity induced by IAA in cerebellar granule cells and displayed a superior neuroprotective effect compared to combination of the iron chelator deferiprone and the radical scavenger LY-231617 in two models of chemically induced cell toxicity: the IAA cell toxicity assay and an H_2O_2 cell toxicity assay. Potentially useful for the treatment of neurodegenerative disorders including stroke, traumatic brain injury, Parkinson's disease and Alzheimer's disease.

SOURCE – Vernalis Research.

REFERENCES

1. Bebbington, D. et al. (Vernalis Research Ltd.) *Ortho-hydroxypyridinone derivs. as iron chelating and antioxidant agents*. EP 1027335, WO 9923075.
2. Bebbington, D. et al. *3,5-Disubstituted-4-hydroxyphenyls linked to 3-hydroxy-2-methyl-4(1H)-pyridinone: Potent inhibitors of lipid peroxidation and cell toxicity*. J Med Chem 2000, 43(15): 2779.

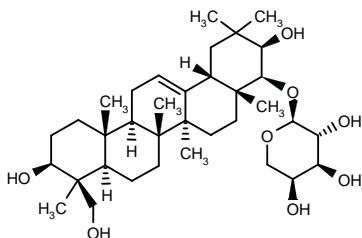
*Identified compound **276705** Drug Data Rep 1999, 021(07): 0588.

MK800-62F1

291262

(3 β ,4 β ,4a β ,6a α ,6b β ,8a α ,9 β ,10 β ,12a β ,12b α ,14b β)-4-(α -L-Arabinopyranosyloxy)-9-(hydroxymethyl)-2,2,4a,6a,6b,9,12a-heptamethyl-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydricene-3,10-diol

22 β -(α -L-Arabinopyranosyloxy)-5- α -olean-12-en-3 β ,21 β ,23-triol



C35 H58 O8; Mol wt: 606.8352

White powder, *m.p.* > 200 °C; $[\alpha]_D^{22} +65^\circ$ (*c* 1, pyridine).

ACTION – Apoptosis inhibitor, a compound extracted from the fermentation broth of *Streptomyces diastatochromogenes* MK800-62F1, proven to inhibit H_2O_2 -induced apoptosis in both human small cell lung carcinoma Ms-1 cells and human T-cell leukemia Jurkat cells. Compound also inhibited camptothecin-induced apoptosis in Jurkat cells. It did not exhibit antioxidant activity *in vitro*. Potentially useful for the treatment of neurodegenerative and inflammatory diseases.

SOURCES – Keio University, Yokohama (JP); Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

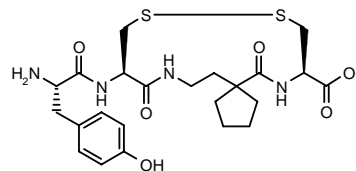
1. Yoshimoto, Y. et al. *MK800-62F1, a new inhibitor of apoptotic cell death, from Streptomyces diastatochromogenes MK800-62F1. II. Structure elucidation*. J Antibiot 2000, 53(6): 575.
2. Yoshimoto, Y. et al. *MK800-62F1, a new inhibitor of apoptotic cell death, from Streptomyces diastatochromogenes MK800-62F1. I. Taxonomy, fermentation, isolation, physico-chemical properties and biological activity*. J Antibiot 2000, 53(6): 569.

RESPIRATORY DRUGS

ASTHMA THERAPY

290368

L-Tyrosyl-L-cysteinyl-1-(2-aminoethyl)cyclopentane-carbonyl-L-cysteine cyclic (2-4)-disulfide



C23 H32 N4 O6 S2; Mol wt: 524.6598

ACTION – Potent cyclic peptide VCAM/VLA-4 antagonist ($IC_{50} = 0.5$ and 24 nM in solid-phase and cell-based assays, respectively). Potentially useful for the treatment of asthma and rheumatoid arthritis.

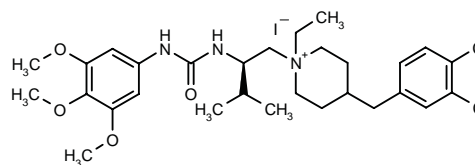
SOURCE – Roche.

REFERENCES

1. Fotouhi, N. et al. *The design and synthesis of potent cyclic peptide VCAM-VLA-4 antagonists incorporating an achiral Asp-Pro mimetic*. Bioorg Med Chem Lett 2000, 10(11): 1171.

290483

4-(3,4-Dichlorobenzyl)-1-ethyl-1-[3-methyl-2(*R*)-[3-(3,4,5-trimethoxyphenyl)ureido]butyl]piperidinium iodide



C29 H42 Cl2 I N3 O4; Mol wt: 694.4738

ACTION – CCR3 receptor antagonist that inhibits the binding of eotaxin to the CCR3 receptor and is thereby potentially useful for the treatment of eosinophil-induced diseases such as asthma. It exhibited an IC_{50} value of $0.21 \mu M$ in a binding assay using CCR3-transfected cells.

ACTION – Neuroprotective agent with potent inhibitory activity against lipid peroxidation in rat brain homogenates ($IC_{50} = 1.0 \mu M$) and the ability to protect cerebellar granule cells from iodoacetate (IAA)-induced toxicity ($EC_{50} = 0.3 \mu M$), being more potent than deferiprone, BHT, trolox and LY-231617 ($EC_{50} = 46.7, 6.0, 77.8$ and $5.0 \mu M$, respectively). Compound also inhibited oxidative stress resulting from neural toxicity induced by IAA in cerebellar granule cells and displayed a superior neuroprotective effect compared to combination of the iron chelator deferiprone and the radical scavenger LY-231617 in two models of chemically induced cell toxicity: the IAA cell toxicity assay and an H_2O_2 cell toxicity assay. Potentially useful for the treatment of neurodegenerative disorders including stroke, traumatic brain injury, Parkinson's disease and Alzheimer's disease.

SOURCE – Vernalis Research.

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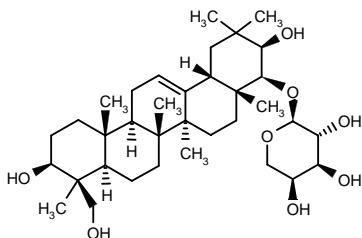
*Identified compound **276705** Drug Data Rep 1999, 021(07): 0588.

MK800-62F1

291262

(3 β ,4 β ,4a β ,6a α ,6b β ,8a α ,9 β ,10 β ,12a β ,12b α ,14b β)-4-(α -L-Arabinopyranosyloxy)-9-(hydroxymethyl)-2,2,4a,6a,6b,9,12a-heptamethyl-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydricene-3,10-diol

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SOURCES – Keio University, Yokohama (JP); Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

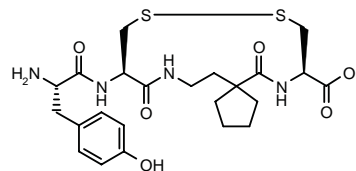
1. Yoshimoto, Y. et al. *MK800-62F1, a new inhibitor of apoptotic cell death, from Streptomyces diastatochromogenes MK800-62F1. II. Structure elucidation*. J Antibiot 2000, 53(6): 575.
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RESPIRATORY DRUGS

ASTHMA THERAPY

290368

L-Tyrosyl-L-cysteinyl-1-(2-aminoethyl)cyclopentane-carbonyl-L-cysteine cyclic (2-4)-disulfide



C23 H32 N4 O6 S2; Mol wt: 524.6598

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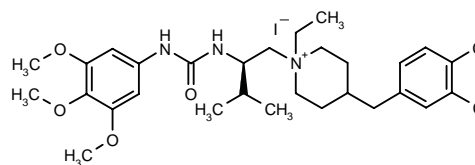
SOURCE – Roche.

REFERENCES

1. Fotouhi, N. et al. *The design and synthesis of potent cyclic peptide VCAM-VLA-4 antagonists incorporating an achiral Asp-Pro mimetic*. Bioorg Med Chem Lett 2000, 10(11): 1171.

290483

4-(3,4-Dichlorobenzyl)-1-ethyl-1-[3-methyl-2(*R*)-[3-(3,4,5-trimethoxyphenyl)ureido]butyl]piperidinium iodide



C29 H42 Cl2 I N3 O4; Mol wt: 694.4738

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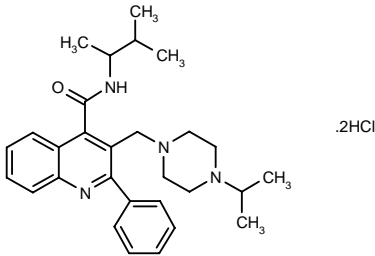
SOURCE – Roche.

REFERENCES

1. Hirschfeld, D.R. et al. (F. Hoffmann-La Roche AG) *Piperidine CCR-3 receptor antagonists*. DE 19955793, GB 2343894, WO 0031033.

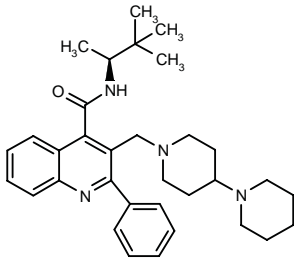
290562

N-(1,2-Dimethylpropyl)-3-(4-isopropylpiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxamide dihydrochloride



C29 H38 N4 O . 2HCl; Mol wt: 531.5680

ACTION – Tachykinin NK₂ and NK₃ receptor antagonist with potential in the treatment and prevention of a wide variety of clinical conditions characterized by over-stimulation of these tachykinin receptors including respiratory diseases, inflammatory disorders, neurogenic inflammation, allergies, ophthalmic diseases, skin disorders, immunological disorders, gastrointestinal disorders, urinary incontinence and renal disorders. Another exemplified compound from this series of quinoline-4-carboxamides is:



290563: C33 H44 N4 O

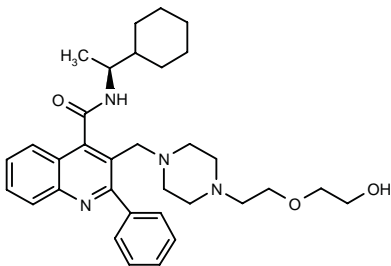
SOURCE – SmithKline Beecham.

REFERENCES

1. Farina, C. et al. (SmithKline Beecham SpA) *Quinoline derivs. as NK-2 and NK-3 receptor ligands*. WO 0031038.

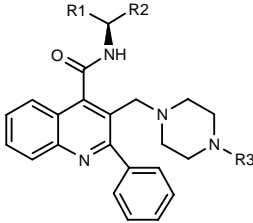
290564

N-[1(*S*)-Cyclohexylethyl]-3-[4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-ylmethyl]-2-phenylquinoline-4-carboxamide

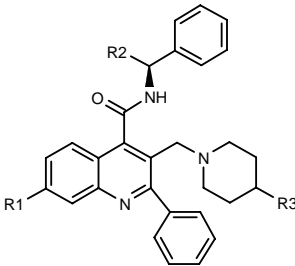


C33 H44 N4 O3; Mol wt: 544.7356

ACTION – Tachykinin NK₂ and NK₃ receptor antagonist with potential in the treatment and prevention of a wide variety of clinical conditions characterized by over-stimulation of these tachykinin receptors including respiratory diseases, inflammatory disorders, neurogenic inflammation, allergies, ophthalmic diseases, skin disorders, immunological disorders, gastrointestinal disorders, urinary incontinence and renal disorders. Other specifically claimed compounds from this series of quinoline-4-carboxamides are:



Compound	R1	R2	R3	Formula
290566	cyclohexyl	Me	CH2CH2OH	C ₃₁ H ₄₀ N ₄ O ₂
290567	Ph	Me	1-Me-4-Pip	C ₃₅ H ₄₁ N ₅ O
290568	cyclohexyl	Me	1-Me-4-Pip	C ₃₅ H ₄₇ N ₅ O
290569	cyclohexyl	Me	H	C ₂₉ H ₃₆ N ₄ O
290570	cyclohexyl	Me	COCH2N(Me)2	C ₃₃ H ₄₃ N ₅ O ₂
290571	cyclohexyl	Me	COCH2CH2N(Et)2	C ₃₆ H ₄₉ N ₅ O ₂
290572	cyclohexyl	Me	4-Me-1-Piz-CH2CO	C ₃₆ H ₄₈ N ₆ O ₂
290573	cyclohexyl	Me	C[N(Me)2]=N(Me)2 ⁺	C ₃₄ H ₄₇ F ₆ N ₆ OP
290577	cyclohexyl	Me	1-pyrrolidinyl-C(=NMe)	C ₃₅ H ₄₆ N ₆ O
290579	Ph	i-Pr	COCH2CH2N(Et)2	C ₃₈ H ₄₇ N ₅ O ₂
290580	cyclohexyl	Me	1-pyrrolidinyl-C(=CHNO2)	C ₃₅ H ₄₄ N ₆ O ₃



Compound	R1	R2	R3	Formula
290574	H	Me	NH2	C30H32N4O
290575	H	Me	4-Me-1-Piz	C35H41N5O
290576	OMe	Me	1-Pip	C36H42N4O2
290578	H	i-Pr	1-Pip	C37H44N4O
290581	OH	Et	1-Pip	C36H42N4O2

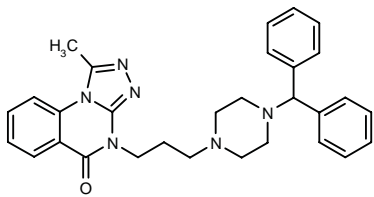
SOURCE – SmithKline Beecham.

REFERENCES

1. Farina, C. et al. (SmithKline Beecham SpA) *Quinoline-4-carboxamide derivs. as NK-3 and NK-2 receptor antagonists*. WO 0031037.

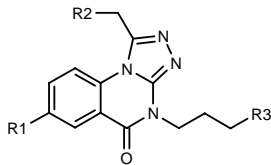
291022

4-[3-[4-(Diphenylmethyl)piperazin-1-yl]propyl]-1-methyl[1,2,4]triazolo[4,3-a]quinazolin-5(4*H*)-one



C30 H32 N6 O; Mol wt: 492.6238

ACTION – Chemokine, especially CCR3, receptor antagonist with potential for the treatment of allergic diseases such as bronchial asthma and atopic dermatitis, inflammatory disorders such as rheumatoid arthritis, autoimmune diseases including nephritis and ulcerative colitis, and AIDS. Antagonist activity at CCR3 and CCR1 receptors was demonstrated in functional assays by IC₅₀ values of 0.3 and 4.1 μM, respectively, against eotaxin- and RANTES-stimulated increase in calcium levels in human eosinophils and THP-1 cells, while no effect was observed at CCR2 receptors (IC₅₀ > 160 μM against MCP-1-stimulated increase in calcium levels in THP-1 cells). Other exemplified compounds from this series of triazolo derivatives include the following:



Compound	R1	R2	R3	Formula
291023	H	H	3-(3-indolyl)-1-Pip	C ₂₆ H ₂₈ N ₆ O
291024	H	H	4-(2-Ph-Ph)-1-Piz	C ₂₉ H ₃₀ N ₆ O
291025	H	Et	4-[(Ph)2CH]-1-Piz	C ₃₂ H ₃₆ N ₆ O
291026	Cl	H	4-[(Ph)2CH]-1-Piz	C ₃₀ H ₃₁ ClN ₆ O

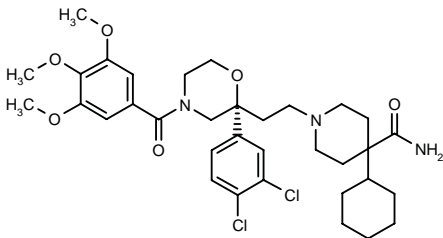
SOURCE – Toray.

REFERENCES

1. Takahashi, T. et al. (Toray Industries, Inc.) *Triazolo derivs. and chemokine inhibitors containing the same as the active ingredient*. WO 0034278.

291090

4-Cyclohexyl-1-[2-[2(*R*)-(3,4-dichlorophenyl)-4-(3,4,5-trimethoxybenzoyl)morpholin-2-yl]ethyl]piperidine-4-carboxamide



C34 H45 Cl2 N3 O6; Mol wt: 662.6505

ACTION – Potent tachykinin NK₁, NK₂ and NK₃ receptor antagonist (IC₅₀ = 9.0 ng/ml in an NK₂ receptor binding assay using guinea pig ileum membrane preparations), expected to be of use for the treatment of chronic obstructive pulmonary disease, bronchitis, asthma, ulcerative colitis and urinary incontinence, among others.

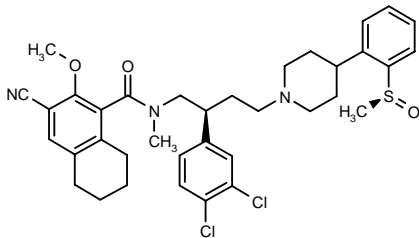
SOURCE – Sankyo.

REFERENCES

1. Nishi, T. et al. (Sankyo Co., Ltd.) *Cyclohexylpiperidine derivs.* JP 2000229968, WO 0034274.

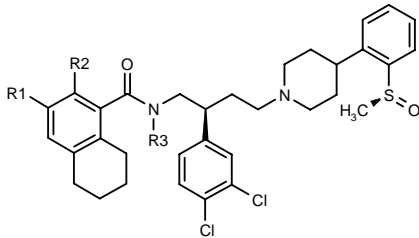
291306

3-Cyano-*N*-[2(*S*)-(3,4-dichlorophenyl)-4-[4-[2-[(*S*)-methylsulfinyl]phenyl]piperidin-1-yl]butyl]-2-methoxy-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide

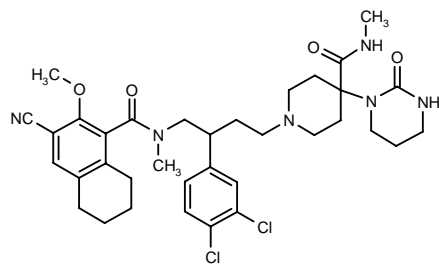


C36 H41 Cl2 N3 O3 S; Mol wt: 666.7099

ACTION – Tachykinin NK₁ and NK₂ receptor antagonist for the treatment of asthma, anxiety, depression, emesis and urinary incontinence. In *in vitro* functional assays, the compound antagonized the action of direct-acting agonists at these receptors. This compound also exhibited marked activity as an NK₁ antagonist when tested for inhibition of bronchoconstriction induced by direct-acting NK₁ agonists in anesthetized guinea pigs. Other compounds from this series of *N*-(2-phenyl-4-piperidinybutyl)-5,6,7,8-tetrahydronaphthalene-1-carboxamides are:



Compound	R1	R2	R3	Formula
291336	CN	H	Me	C ₃₅ H ₃₉ Cl ₂ N ₃ O ₂ S
291338	CN	Me	Me	C ₃₆ H ₄₁ Cl ₂ N ₃ O ₂ S
291340	CN	Et	Me	C ₃₇ H ₄₃ Cl ₂ N ₃ O ₂ S
291342	OMe	Me	Me	C ₃₆ H ₄₄ Cl ₂ N ₃ O ₃ S
291344	Me	OMe	Me	C ₃₆ H ₄₄ Cl ₂ N ₃ O ₃ S
291347	CN	OMe	SO ₂ Me	C ₃₆ H ₄₁ Cl ₂ N ₃ O ₅ S ₂



291349: C35 H44 Cl2 N6 O4

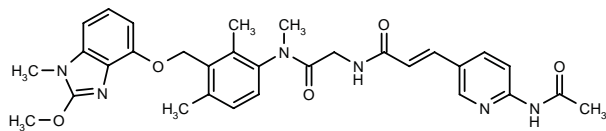
*s***SOURCE** – AstraZeneca.

REFERENCES

1. Ohnmacht, C.J. (AstraZeneca U.K., Ltd.) *N*-(2-Phenyl-4-piperidinybutyl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamides and their use as neurokinin 1 (NK₁) and/or neurokinin 2 (NK₂) receptor antagonists. WO 0034243.

291315

3-(6-Acetamidopyridin-3-yl)-*N*-[*N*-[3-(2-methoxy-1-methyl-1*H*-benzimidazol-4-yloxy)methyl]-2,4-dimethylphenyl]-*N*-methylcarbamoylmethyl]-2(*E*)-propenamide



C31 H34 N6 O5; Mol wt: 570.6466

ACTION – Bradykinin antagonist, a specifically claimed compound from a series of benzimidazole derivatives with potential in the treatment or prevention of diseases mediated by bradykinin and its analogues such as allergy, inflammation, autoimmune diseases, shock and pain.

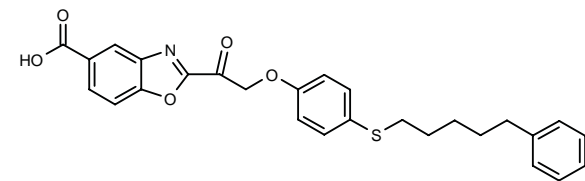
SOURCE – Fujisawa.

REFERENCES

1. Oku, T. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Benzimidazole cpds. as bradykinin antagonists*. US 6083961, WO 9604251.

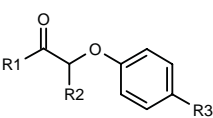
291332

2-[2-[4-(5-Phenylpentylsulfanyl)phenoxy]acetyl]-benzoxazole-5-carboxylic acid



C27 H25 N O5 S; Mol wt: 475.5625

ACTION – Antiinflammatory agent found to inhibit the release of [³H]-arachidonic acid from DMSO-differentiated HL-60 cells in response to calcium ionophore challenge (IC₅₀ < 10 μM). Potentially useful for the treatment of asthma. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
291333	4-Me-5-(HOCH2CH2)-2-thiazolyl	H	S(CH2)5Ph	C ₂₅ H ₂₉ NO ₃ S ₂
291334	6-CO2H-2-benzothiazolyl	H	S(CH2)5Ph	C ₂₇ H ₂₅ NO ₄ S ₂
291335	4-Me-5-(HOCH2CH2)-2-thiazolyl	H	3,5-(Cl)2-Ph-CH2O	C ₂₁ H ₁₉ Cl ₂ NO ₄ S
291337	4-Me-5-(HOCH2CH2)-2-thiazolyl	H	SCH2Ph	C ₂₁ H ₂₁ NO ₃ S ₂
291339	2-benzothiazolyl	H	SO2(CH2)5Ph	C ₂₆ H ₂₅ NO ₄ S ₂
291341	4-Me-5-(HOCH2CH2)-2-thiazolyl	H	3,5-(Cl)2-Ph-CH2SO2	C ₂₁ H ₁₉ Cl ₂ NO ₅ S ₂
291343	5-CO2H-2-benzoxazolyl	H	3,5-(Cl)2-Ph-CH2S	C ₂₃ H ₁₅ Cl ₂ NO ₄ S
291345	4-Me-5-(CO2HCH2CH2)-2-thiazolyl	H	S(CH2)5Ph	C ₂₆ H ₂₉ NO ₄ S ₂
291346	4-Me-5-[CO2H(CH2)3]-2-thiazolyl	Ph	S(CH2)5Ph	C ₃₃ H ₃₅ NO ₄ S ₂
291348	2-Pyr	H	S(CH2)5Ph	C ₂₄ H ₂₅ NO ₂ S

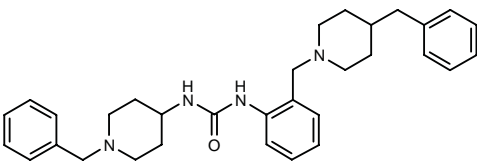
SOURCE – AstraZeneca.

REFERENCES

1. Connolly, S. and Mete, A. (AstraZeneca U.K., Ltd.;AstraZeneca AB) *Novel cpds*. WO 0034254.

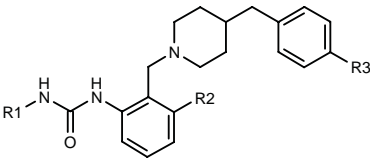
291436

N-(1-Benzylpiperidin-4-yl)-*N*'-[2-(4-benzylpiperidin-1-yl-methyl)phenyl]urea

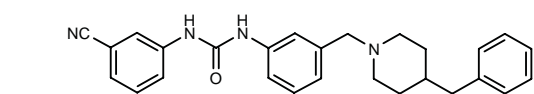


C32 H40 N4 O; Mol wt: 496.6950

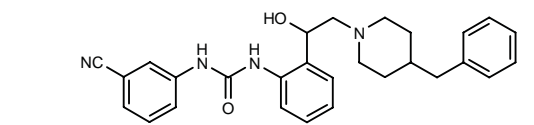
ACTION – Chemokine CCR3 receptor modulator with potential for the treatment or prevention of a broad range of disorders including asthma, allergic disorders, atopic dermatitis and inflammatory bowel disease. Other specifically claimed compounds from this series of *N*-ureidoalkyl-piperidines include the following:



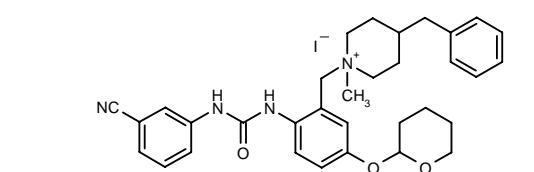
Compound	R1	R2	R3	Formula
291437	CH2CH(Ph)2	H	H	C ₃₄ H ₃₇ N ₃ O
291439	3-CN-Ph	CONHMe	F	C ₂₉ H ₃₀ FN ₃ O ₂
291440	3-Ac-Ph	CONHPh	F	C ₃₅ H ₃₅ FN ₃ O ₃



291438: C27 H28 N4 O



291441: C28 H30 N4 O2



291443: C33 H39 I N4 O3

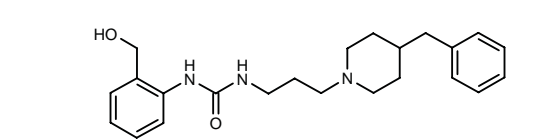
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Ko, S.S. et al. (DuPont Pharmaceuticals Co.) *N-Ureidoalkyl-piperidines as modulators of chemokine receptor activity*. WO 0035454.

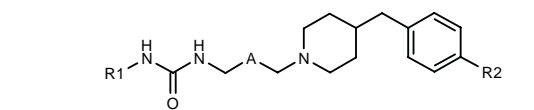
291444

N-[3-(4-Benzylpiperidin-1-yl)propyl]-N'-[2-(hydroxymethyl)phenyl]urea

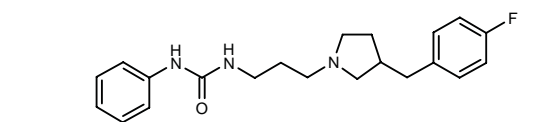


C23 H31 N3 O2; Mol wt: 381.5169

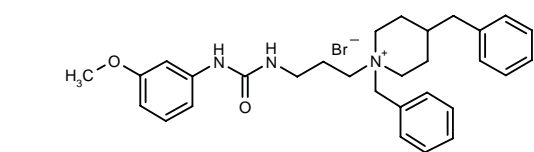
ACTION – Chemokine CCR3 receptor modulator with potential for the treatment or prevention of a broad range of disorders including asthma, allergic disorders, atopic dermatitis and inflammatory bowel disease. Other specifically claimed compounds from this series of *N*-ureidoalkyl-piperidines include the following:



Compound	R1	R2	A	Formula
291445	3-I-Ph	H	-CH2-	C ₂₂ H ₂₈ IN ₃ O
291446	cyclohexyl	F	-CH2-	C ₂₂ H ₃₄ FN ₃ O
291447	2-i-Pr-Ph	F	-CH2-	C ₂₅ H ₃₄ FN ₃ O
291448	3,5-(Ac)2-Ph	F	-CH2-	C ₂₆ H ₃₂ FN ₃ O ₃
291451	4-F-Ph	F	-(CH2)2-	C ₂₃ H ₂₉ F ₂ N ₃ O
291452	3-Ac-Ph	H	-ethynylene-	C ₂₅ H ₂₉ N ₃ O ₂



291449: C21 H26 F N3 O



291450: C30 H38 Br N3 O2

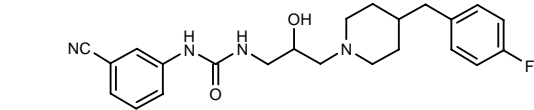
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Ko, S.S. et al. (DuPont Pharmaceuticals Co.) *N-Ureidoalkyl-piperidines as modulators of chemokine receptor activity*. WO 0035451.

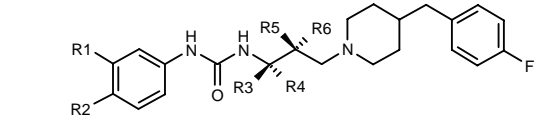
291453

N-(3-Cyanophenyl)-N'-[3-[4-(4-fluorobenzyl)piperidin-1-yl]-2-hydroxypropyl]urea



C23 H27 F N4 O2; Mol wt: 410.4903

ACTION – Chemokine CCR3 receptor modulator with potential for the treatment or prevention of a broad range of disorders including asthma, allergic disorders, atopic dermatitis and inflammatory bowel disease. Other specifically claimed compounds from this series of *N*-ureidoalkyl-piperidines include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
291454	OMe	H	CH2Ph	H	H	OH	C ₃₀ H ₃₅ FN ₃ O ₃
291455	Ac	H	H	H	Me	OH	C ₂₅ H ₃₂ FN ₃ O ₃
291460	Ac	H	H	H	i-Pr	OH	C ₂₇ H ₃₆ FN ₃ O ₃
291461	Ac	H	CH2Ph	H	H	OH	C ₃₁ H ₃₆ FN ₃ O ₃
291462	Ac	H	Me	H	H	OH	C ₂₅ H ₃₂ FN ₃ O ₃
291463	CN	H	H	Et	OH	H	C ₂₅ H ₃₁ FN ₄ O ₂
291464	H	F	i-Pr	H	H	OH	C ₂₅ H ₃₃ F ₂ N ₃ O ₂

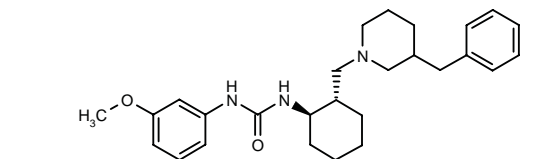
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Ko, S. et al. (DuPont Pharmaceuticals Co.) *N-Ureidoalkyl-piperidines as modulators of chemokine receptor activity*. WO 0035453.

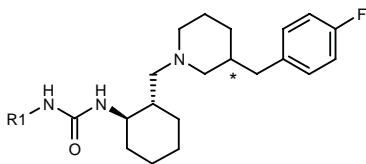
291470

trans-N'-[2-(3-benzylpiperidin-1-ylmethyl)cyclohexyl]-N'- (3-methoxyphenyl)urea

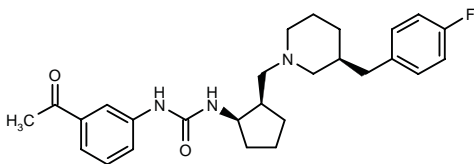


C27 H37 N3 O2; Mol wt: 435.6083

ACTION – Chemokine CCR3 receptor modulator with potential for the treatment or prevention of a broad range of disorders including asthma, allergic disorders, atopic dermatitis and inflammatory bowel disease. Other specifically claimed compounds from this series of *N*-ureidoalkyl-piperidines include the following:



Compound	R1	*Isomer	Formula
291471	4-F-Ph	S	C ₂₆ H ₃₃ F ₂ N ₃ O
291472	4-Cl-2-benzothiazolyl	S	C ₂₇ H ₃₂ ClFN ₄ OS
291473	3,5-(1-Me-5-tetrazolyl)2-Ph	S	C ₃₀ H ₃₈ FN ₁₁ O
291474	3,4,5-(MeO)3-Ph	S	C ₂₉ H ₄₀ FN ₃ O ₄
291475	3-OH-4-MeO-Ph	R	C ₂₇ H ₃₆ FN ₃ O ₃
291476	t-BuCH2C(Me)2	S	C ₂₈ H ₄₆ FN ₃ O



291477: C27 H34 F N3 O2

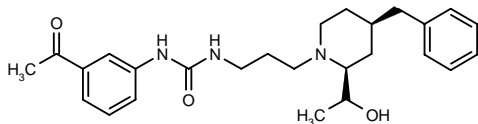
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Ko, S.S. et al. (DuPont Pharmaceuticals Co.) *N-Ureidoalkyl-piperidines as modulators of chemokine receptor activity*. WO 0035452.

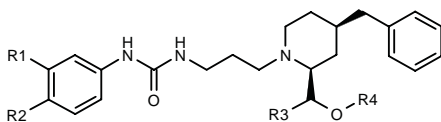
291478

cis-N-(3-Acetylphenyl)-*N'*-[3-[4-benzyl-2-(1-hydroxyethyl)-piperidin-1-yl]propyl]urea



C26 H35 N3 O3; Mol wt: 437.5805

ACTION – Chemokine CCR3 receptor modulator with potential for the treatment or prevention of a broad range of disorders including asthma, allergic disorders, atopic dermatitis and inflammatory bowel disease. Other specifically claimed compounds from this series of *N*-ureidoalkyl-piperidines include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
291479	Ac	H	Et	H		C ₂₇ H ₃₇ N ₃ O ₃
291480	Ac	H	Pr	H		C ₂₈ H ₃₉ N ₃ O ₃
291481	Ac	H	Bu	H		C ₂₉ H ₄₁ N ₃ O ₃

Compound	R1	R2	R3	R4	Isomer	Formula
291482	Ac	H	i-Pr	H		C ₂₈ H ₃₉ N ₃ O ₃
291483	Ac	H	Bu	H	(+)	C ₂₉ H ₄₁ N ₃ O ₃
291484	-CH=NNH-		Bu	H		C ₂₈ H ₃₉ N ₅ O ₂
291485	Ac	H	Et	3-Ac-PhNHCO		C ₃₆ H ₄₄ N ₄ O ₅
291486	Ac	H	Pr	3-Ac-PhNHCO		C ₃₇ H ₄₆ N ₄ O ₅
291487	Ac	H	Bu	3-Ac-PhNHCO		C ₃₈ H ₄₈ N ₄ O ₅
291488	Ac	H	i-Pr	3-Ac-PhNHCO		C ₃₇ H ₄₆ N ₄ O ₅
291489	Ac	H	i-Bu	3-Ac-PhNHCO		C ₃₈ H ₄₈ N ₄ O ₅

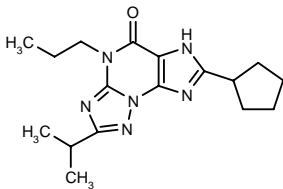
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Ko, S.S. et al. (DuPont Pharmaceuticals Co.) *N-Ureidoalkyl-piperidines as modulators of chemokine receptor activity*. WO 0035449.

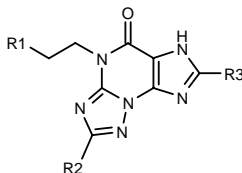
291544

7-Cyclopentyl-2-isopropyl-4-propyl-5,6-dihydro-4*H*-[1,2,4]triazolo[5,1-*b*]purin-5-one



C17 H24 N6 O; Mol wt: 328.4176

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor giving an IC₅₀ value of 0.018 μM when tested for PDE4 inhibition using enzyme from human U937 cells. It is expected to be of use for treating allergic and inflammatory disorders, particularly asthma and chronic obstructive pulmonary disease. Other exemplified tricyclic nitrogen heterocycles are:



Compound	R1	R2	R3	Formula
291546	Me	Et	cyclopentyl	C ₁₆ H ₂₂ N ₆ O
291547	H	4-MeO-PhCH2	t-Bu	C ₂₀ H ₂₄ N ₆ O ₂
291548	H	CH2CH2Ph	cyclopentyl	C ₂₁ H ₂₄ N ₆ O
291549	H	CH2Ph	3-THF	C ₁₉ H ₂₀ N ₆ O ₂
291550	Me	Pr	cyclopentyl	C ₁₇ H ₂₄ N ₆ O
291551	H	CH2Ph	t-Bu	C ₁₉ H ₂₂ N ₆ O
291552	Me	Pr	Ph	C ₁₈ H ₂₀ N ₆ O
291553	H	CH2Ph	cyclopentyl	C ₂₀ H ₂₂ N ₆ O
291554	Me	CH2Ph	Pr	C ₁₉ H ₂₂ N ₆ O
291555	H	1-pyrrolyl-CH2	cyclopentyl	C ₁₈ H ₂₁ N ₇ O
291556	Me	CH2Ph	cyclopentyl	C ₂₁ H ₂₄ N ₆ O
291557	Me	t-Bu	cyclopentyl	C ₁₈ H ₂₆ N ₆ O
291558	Me	Bu	cyclopentyl	C ₁₈ H ₂₆ N ₆ O

SOURCE – Boehringer Ingelheim.

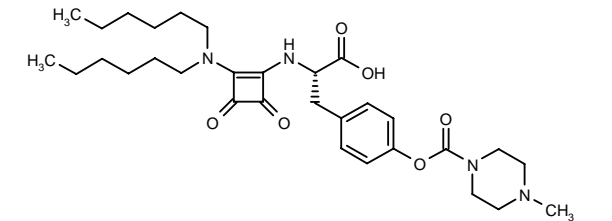
REFERENCES

1. Hoffmann, M. et al. (Boehringer Ingelheim Pharma KG) *Tricyclic nitrogen heterocycles as PDE IV inhibitors*. DE 19858331, WO 0035428.

291632

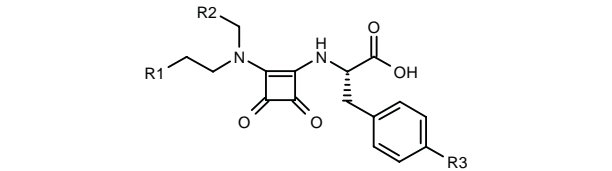
2(*S*)-[2-(Dihexylamino)-3,4-dioxo-1-cyclobuten-1-yl-amino]-3-[4-(4-methylpiperazin-1-yl)carboxyphenyl]-propionic acid

N-[2-(Dihexylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-*O*-(4-methylpiperazin-1-ylcarbonyl)-L-tyrosine



C31 H46 N4 O6; Mol wt: 570.7264

ACTION – Inhibitor of leukocyte adhesion mediated by $\alpha_4\beta_1$ integrin (VLA-4), as demonstrated in a monovalent fluorescence-activated cell sorter (FACS) assay, inhibiting the interaction of soluble VCAM-1 with Jurkat cells expressing VLA-4 integrin with an IC_{50} of 0.2 nM. Potentially useful for the treatment of inflammatory and autoimmune diseases and specifically claimed for treating multiple sclerosis, meningitis, asthma, Alzheimer’s disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel syndrome, rheumatoid arthritis, tumor metastasis, tissue transplantation and myocardial ischemia. Other exemplified compounds from this series of 3,4-diamino-3-cyclobutene-1,2-dione derivatives are:



Compound	R1	R2	R3	Formula
291638	Bu	C5H11	H	C ₂₅ H ₃₆ N ₂ O ₄
291639	Ph	H	4-Pyr-CONH	C ₂₈ H ₂₆ N ₄ O ₅
291640	Bu	C5H11	4-Pyr-CONH	C ₃₁ H ₄₀ N ₄ O ₅
291641	Ph	H	OCON(Me)2	C ₂₅ H ₂₇ N ₃ O ₆
291642	Bu	C5H11	OCON(Me)2	C ₂₈ H ₄₁ N ₃ O ₆
291643	4-Pyr	H	OCON(Me)2	C ₂₄ H ₂₆ N ₄ O ₆
291644	Ph	H	4-Me-1-Piz-COO	C ₂₈ H ₃₂ N ₄ O ₆
291645	4-Pyr	H	4-Me-1-Piz-COO	C ₂₇ H ₃₁ N ₅ O ₆

SOURCE – American Home Products.

REFERENCES

1. Lombardo, L.J. and Sabalski, J.E. (American Home Products Corp.) *3,4-Diamino-3-cyclobutene-1,2-dione derivs. which inhibit leukocyte adhesion mediated by VLA-4*. WO 0035855.

K-5993

291017

Cyclo(Val-Val-Xaa-Val-Val-D-Ala), where Xaa is the residue of a natural amino acid other than Cys or Trp

ACTION – A selective inhibitor of the binding of IL-4 to the IL-4 receptor, with potential for the treatment or prevention of allergic disorders and viral, bacterial, parasitic and fungal infections. *In vitro*, compound was shown to inhibit the binding of biotinylated human and murine IL-4 to their respective receptors, as well as to inhibit IL-4-induced proliferation, while having no significant effect in an IL-1 binding assay or against human IL-1 β -induced proliferation. Other compounds from this series of cyclohexapeptides include the following:

Cyclo(Val-Tyr-Xaa-Val-Tyr-D-Ala), where Xaa is the residue of a natural amino acid other than Cys or Trp

K-0021 [291018]

Cyclo(Tyr-Val-Xaa-Tyr-Val-D-Ala), where Xaa is the residue of a natural amino acid other than Cys or Trp

K-0022 [291019]

SOURCE – Aventis Pharma.

REFERENCES

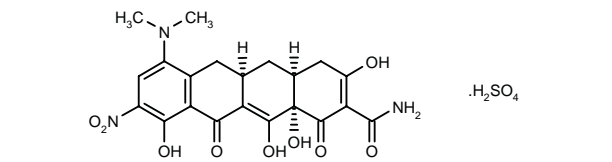
1. Henke, S. et al. (Aventis Pharma AG) *Cyclohexapeptides and their mixtures, a process for preparing them, and their use*. US 6080719.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

290394

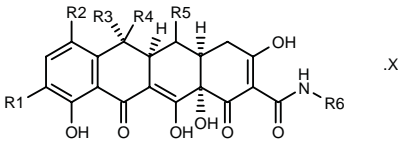
(4*aS*,5*aR*,12*aS*)-7-(Dimethylamino)-3,10,12,12*a*-tetrahydroxy-9-nitro-1,11-dioxo-1,4,4*a*,5,5*a*,6,11,12*a*-octahydronaphthacene-2-carboxamide sulfate

4-De(dimethylamino)-7-(dimethylamino)-6-demethyl-6-deoxy-9-nitrotetracycline sulfate



C21 H21 N3 O9 . H2 O4 S; Mol wt: 557.4867

ACTION – A representative compound from a series of chemically modified 4-dedimethylaminotetracycline derivatives useful for the treatment of disorders characterized by excessive collagen destruction, excessive matrix metalloproteinase (MMP), TNF, nitric oxide, IL-1 or elastase activity, excessive bone density loss, excessive protein degradation, excessive collagen glycosylation, excessive COX-2 activity, insufficient bone protein synthesis, insufficient IL-10 production or excessive phospholipase A₂ (PLA₂) activity including abdominal aortic aneurysms, corneal ulceration, periodontal disease, diabetes, scleroderma, acute respiratory distress syndrome (ARDS), cystic fibrosis, emphysema, cancer, graft-versus-host disease, thrombocytopenia, spondyloarthropathies, osteoporosis, Paget’s disease, autoimmune diseases, systemic lupus erythematosus, acute or chronic inflammatory conditions, renal diseases and connective tissue diseases. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	R6	X	Formula
290395	N3	N(Me)2	H	H	H	H	H2SO4	C ₂₁ H ₂₁ N ₅ O ₇ ·H ₂ O ₄ S
290396	NH2	H	Me	H	H	H		C ₂₀ H ₂₀ N ₂ O ₇
290397	N(Me)2	H	Me	H	H	H	H2SO4	C ₂₂ H ₂₄ N ₂ O ₇ ·H ₂ O ₄ S
290398	H	N3	Me	H	OH	H		C ₂₀ H ₁₈ N ₄ O ₈
290399	H	N(Et)2	Me	OH	OH	H	H2SO4	C ₂₄ H ₂₈ N ₂ O ₉ ·H ₂ O ₄ S
290400	H	N(Me)2	Me	H	H	H	H2SO4	C ₂₂ H ₂₄ N ₂ O ₇ ·H ₂ O ₄ S
290401	NHCO-C5H11	H	H	H	H	4-Me-1-Piz-CH2		C ₃₁ H ₄₀ N ₄ O ₈

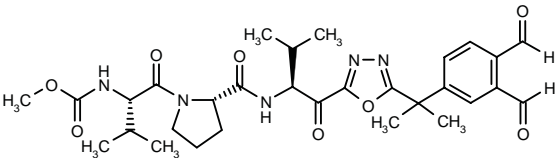
SOURCE – CollaGenex.

REFERENCES

1. Ashley, R.A. and Hlavka, J.J. (CollaGenex Pharmaceuticals, Inc.) *Novel 4-dedimethylaminotetracycline derivs.* WO 0028983.

290972

4-[1-[5-(*N*-Methoxycarbonyl-L-valyl-L-prolyl-L-valyl)-1,3,4-oxadiazol-2-yl]-1-methylethyl]benzene-1,2-dicarb-aldehyde



C30 H39 N5 O8; Mol wt: 597.6651

ACTION – Serine protease inhibitor, especially active against human neutrophil elastase, giving a K_i value of 0.24 nM when tested for inhibition of human sputum-derived elastase and producing 44, 69 and 99% inhibition of elastase *ex vivo* in blood samples from animals previously administered oral doses of 3, 10 and 30 mg/kg, respectively. This compound is expected to be useful for the treatment of adult respiratory distress syndrome, septic shock and multiple organ failure, as well as other elastase-mediated conditions.

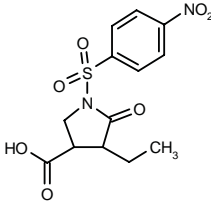
SOURCES – Cortech; Ono.

REFERENCES

1. Spruce, L. et al. (Cortech, Inc.;Ono Pharmaceutical Co., Ltd.) *Peptoid and nonpeptoid containing alpha-keto oxadiazoles as serine protease inhibitors.* WO 0032216.

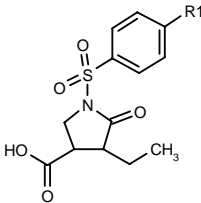
291506

4-Ethyl-1-(4-nitrophenylsulfonyl)-5-oxopyrrolidine-3-carboxylic acid



C13 H14 N2 O7 S; Mol wt: 342.3266

ACTION – An inhibitor of serine proteases such as elastase (K_i = 0.20 ± 0.1 mM), thrombin, factor Xa, trypsin, chymotrypsin and β-lactamases, also reported to be useful as an antibiotic, claimed for the treatment of acute respiratory distress syndrome, cystic fibrosis, emphysema, chronic bronchitis, coagulation disorders and bacterial infections. A representative compound from a series of monocyclic γ-lactams and larger ring lactams, wherein the following compounds are also included:



Compound	R1	Formula
291507	Me	C ₁₄ H ₁₇ NO ₅ S
291508	CF3	C ₁₄ H ₁₄ F ₃ NO ₅ S

SOURCE – Isis Innovation.

REFERENCES

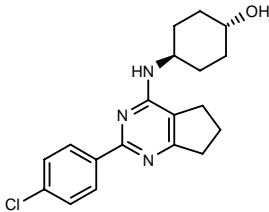
1. Schofield, C.J. (Isis Innovation Ltd.) *Lactams.* WO 0035871.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

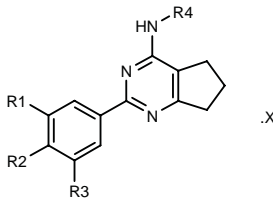
290597

trans-4-[2-(4-Chlorophenyl)-6,7-dihydro-5*H*-cyclopenta-*d*]pyrimidin-4-ylamino)cyclohexanol



C19 H22 Cl N3 O; Mol wt: 343.8558

ACTION – Potent soluble guanylate cyclase (sGC)-activating agent, as demonstrated in an *in vitro* assay by 35-fold stimulation of sGC from bovine lung at a concentration of 50 μM. Potentially useful for the treatment and prophylaxis of disorders associated with low cGMP levels including cardiovascular disorders such as hypertension, angina pectoris, heart failure, thrombosis and atherosclerosis. Other compounds from this series of substituted 4-amino-2-aryl-cyclopenta[*d*]pyrimidines include the following:



Compound	R1	R2	R3	R4	X	Formula
290598	Cl	H	Cl	<i>trans</i> -4-OH-cyclohexyl	MeSO3H	C ₁₉ H ₂₁ Cl ₂ N ₃ O .CH ₄ O ₃ S
290599	Cl	H	H	cyclopentyl		C ₁₈ H ₂₀ ClN ₃
290600	H	Me	H	<i>trans</i> -4-OH-cyclohexyl		C ₂₀ H ₂₅ N ₃ O

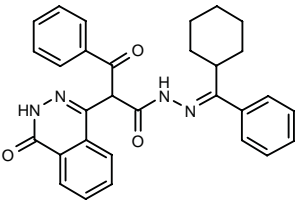
SOURCE – Aventis Pharma.

REFERENCES

1. Schindler, U. et al. (Aventis Pharma Deutschland GmbH) *Substd. 4-amino-2-aryl-cyclopenta[d]pyrimidines, their production and use and pharmaceutical preparations containing same*. DE 19853278, WO 0031047.

291127

N'-[Cyclohexyl(phenyl)methylene]-3-oxo-2-(4-oxo-3,4-dihydrophthalazin-1-yl)-3-phenylpropionohydrazide



C30 H28 N4 O3; Mol wt: 492.5762

ACTION – Endothelin-converting enzyme (ECE) inhibitor (IC₅₀ = 5.6 μM against rat lung enzyme), a repre-sentative compound from a series of amino derivatives with potential in the treatment of circulatory disorders such as hypertension and arteriosclerosis.

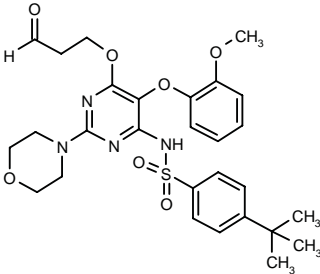
SOURCE – Sumitomo Pharmaceuticals.

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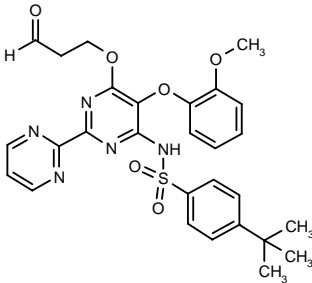
291130

4-*tert*-Butyl-*N*-[6-(2-formylethoxy)-5-(2-methoxyphenoxy)-2-(4-morpholinyl)pyrimidin-4-yl]benzenesulfonamide



C28 H34 N4 O7 S; Mol wt: 570.6636

ACTION – Endothelin antagonist proven to produce 80 and 92% inhibition, respectively, at 10 μM and 22 and 37% inhibition, respectively, at 1 μM in CHO cells expressing human ET_A and ET_B receptors. Potentially useful for the treatment of cardiovascular disorders such as hypertension or cardiopathies. Another exemplified pyrimidine derivative is:



291133: C28 H29 N5 O6 S

SOURCE – Kowa.

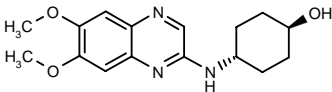
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

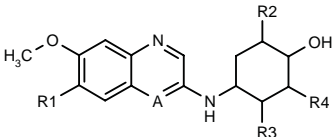
290608

trans-4-(6,7-Dimethoxyquinoxalin-2-ylamino)cyclohexanol



C16 H21 N3 O3; Mol wt: 303.3599

ACTION – Platelet-derived growth factor (PDGF) receptor and/or p56^{lck} tyrosine kinase inhibitor with potential in the treatment of disorders/conditions involving cellular differentiation, proliferation, extracellular matrix production, mediator release and/or T-cell activation and proliferation, particularly restenosis, cancer and inflammation. Other specifically claimed compounds from this series of quinoline and quinoxaline derivatives are:



Compound	R1	R2	R3	R4	A	Isomer	Formula
290609	OMe	H	H	H	N	cis	C ₁₆ H ₂₁ N ₃ O ₃
290610	OMe	Me	H	H	N		C ₁₇ H ₂₃ N ₃ O ₃
290611	OMe	-CH2-	H	H	N	exo,exo	C ₁₇ H ₂₁ N ₃ O ₃
290612	Cl	H	H	H	N	trans	C ₁₅ H ₁₈ ClN ₃ O ₂
290614	OMe	H	H	H	CH		C ₁₇ H ₂₂ N ₂ O ₃
290615	OMe	Me	H	H	N	(-)-1r,2t,4t	C ₁₇ H ₂₃ N ₃ O ₃
290616	OMe	-CH2-	H	H	N	(1S,2R,4S,5R)	C ₁₇ H ₂₁ N ₃ O ₃

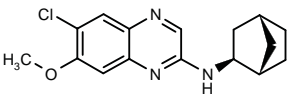
SOURCE – Aventis Pharma.

REFERENCES

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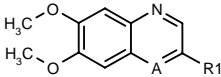
290617

exo-N-(Bicyclo[2.2.1]hept-2-yl)-N-(6-chloro-7-methoxy-quinoxalin-2-yl)amine



C16 H18 Cl N3 O; Mol wt: 303.7912

ACTION – Platelet-derived growth factor (PDGF) receptor and/or p56^{lck} tyrosine kinase inhibitor with potential in the treatment of disorders/conditions involving cellular differentiation, proliferation, extracellular matrix production, mediator release and/or T-cell activation and proliferation, particularly restenosis, cancer and inflammation. Other specifically claimed compounds from this series of quinoline and quinoxaline derivatives include the following:



Compound	R1	A	Formula
290618	(1S,3R)-3-Me-cyclohexyl-NH	CH	C ₁₈ H ₂₄ N ₂ O ₂
290619	3-cyclohexen-1-yl-NH	N	C ₁₆ H ₁₉ N ₃ O ₂
290620	endo-bicyclo[2.2.1]hept-2-yl-NH	N	C ₁₇ H ₂₁ N ₃ O ₂
290621	exo-bicyclo[2.2.1]hept-5-en-2-yl-O	N	C ₁₇ H ₁₈ N ₂ O ₃
290622	cyclopentyl-CH2O	N	C ₁₆ H ₂₀ N ₂ O ₃
290623	(1S,2S,4R)-bicyclo[2.2.1]hept-2-yl-NH	N	C ₁₇ H ₂₁ N ₃ O ₂
290624	trans-4-(CO2Me)-cyclohexyl-NH	N	C ₁₈ H ₂₃ N ₃ O ₄
290625	(1R,3R)-3-Me-cyclohexyl-NH	N	C ₁₇ H ₂₃ N ₃ O ₂

SOURCE – Aventis Pharma.

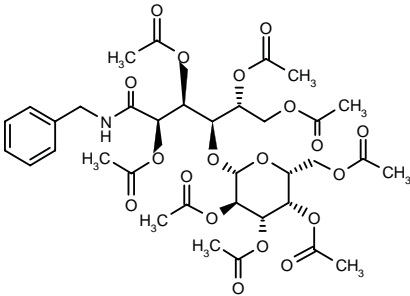
REFERENCES

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290626

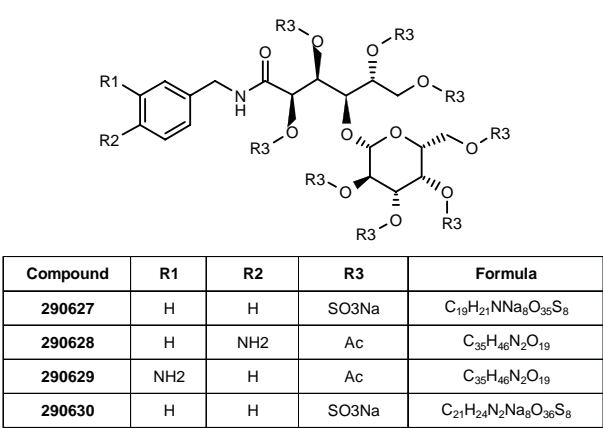
Octa-*O*-acetyl-*N*-benzylactobionamide

2,3,5,6-Tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-*N*-benzyl-D-gluconamide



C35 H45 N O19; Mol wt: 783.7285

ACTION – An inhibitor of smooth muscle cell proliferation (IC₅₀ = 118 μM using porcine smooth muscle cells), potentially useful for the treatment of diseases caused by excessive smooth muscle cell proliferation such as restenosis. Compound is also reported to inhibit angiogenesis and is thus also useful for the treatment of cancer and chronic inflammation. Other exemplified compounds from this series of benzylactobionamides include the following:



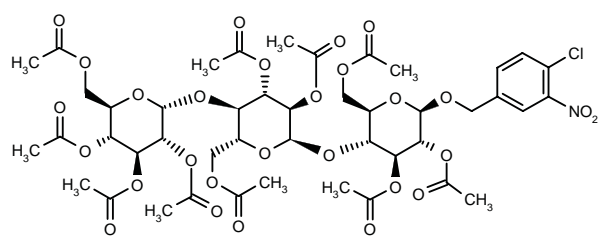
SOURCE – American Home Products.

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1. Mayer, S.C. (American Home Products Corp.) *Benzylactobionamides as inhibitors of smooth muscle cell proliferation*. WO 0031092.

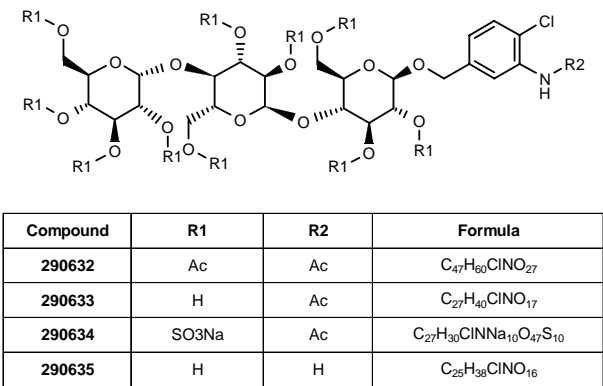
290631

4-Chloro-3-nitrobenzyl deca-*O*-acetyl-β-D-maltotrioside



C45 H56 Cl N O28; Mol wt: 1094.3690

ACTION – An inhibitor of smooth muscle cell proliferation (IC₅₀ = 1.8 μM using porcine smooth muscle cells), potentially useful for the treatment of diseases caused by excessive smooth muscle cell proliferation such as restenosis. Compound is also reported to inhibit angiogenesis and is thus also useful for the treatment of cancer and chronic inflammation. Other exemplified compounds from this series of benzylmaltotriosides include the following:



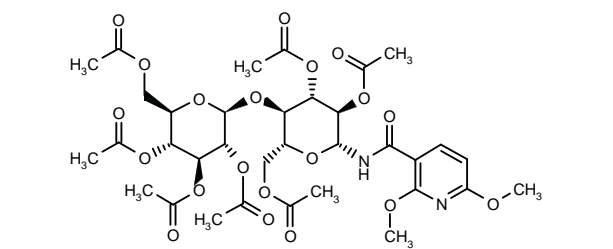
SOURCE – American Home Products.

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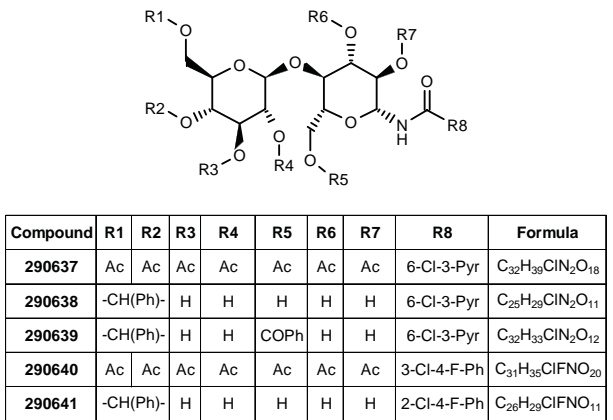
290636

2,6-Dimethoxy-*N*-(hepta-*O*-acetyl-β-D-cellobiosyl)-pyridine-3-carboxamide



C34 H44 N2 O20; Mol wt: 800.7156

ACTION – An inhibitor of smooth muscle cell proliferation (IC₅₀ = 3.11 μM using porcine smooth muscle cells), potentially useful for the treatment of diseases caused by excessive smooth muscle cell proliferation such as restenosis. Compound is also reported to inhibit angiogenesis and is thus also useful for the treatment of cancer and chronic inflammation. Other exemplified compounds from this series of benzylglycosylamides include the following:



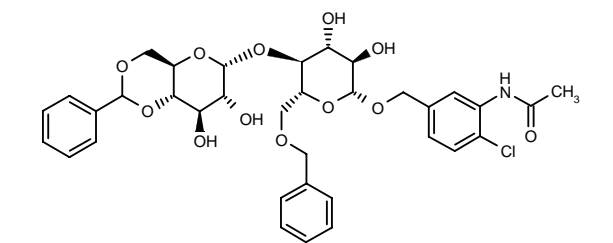
SOURCE – American Home Products.

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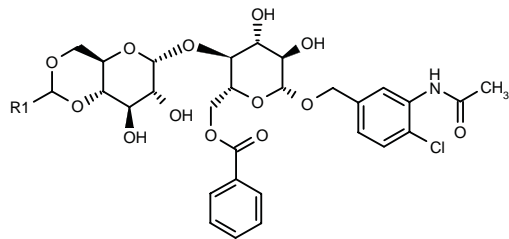
290642

N-[5-(6-*O*-Benzyl-4',6'-*O*-benzylidene-β-D-maltosyloxy-methyl)-2-chlorophenyl]acetamide

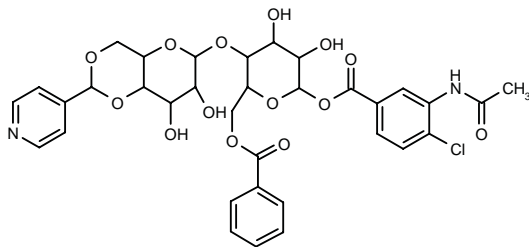


C35 H40 Cl N O12; Mol wt: 702.1490

ACTION – An inhibitor of smooth muscle cell proliferation (IC_{50} = 0.001 μ M using porcine smooth muscle cells), potentially useful for the treatment of diseases caused by excessive smooth muscle cell proliferation such as restenosis. Compound is also reported to inhibit angiogenesis and is thus also useful for the treatment of cancer and chronic inflammation. Other exemplified compounds from this series of acetal benzylmaltosides include the following:



Compound	R1	Formula
290643	4-NO ₂ -Ph	C ₃₅ H ₃₇ ClN ₂ O ₁₅
290644	i-Pr	C ₃₂ H ₄₀ ClNO ₁₃
290645	(R)-CH ₂ CH ₂ CN	C ₃₂ H ₃₇ ClN ₂ O ₁₃



290646: C₃₄ H₃₅ Cl N₂ O₁₄

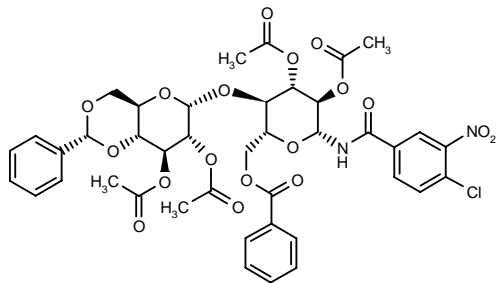
SOURCE – American Home Products.

REFERENCES

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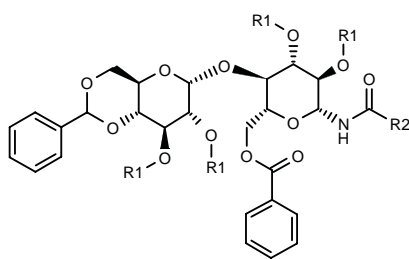
290647

N-[(*R*)-6-*O*-Benzoyl-4',6'-benzylidene- β -D-maltosyl]-4-chloro-3-nitrobenzamide



C₄₁ H₄₁ Cl N₂ O₁₈; Mol wt: 885.2239

ACTION – An inhibitor of smooth muscle cell proliferation (IC_{50} = 0.26 μ M using porcine smooth muscle cells), potentially useful for the treatment of diseases caused by excessive smooth muscle cell proliferation such as restenosis. Compound is also reported to inhibit angiogenesis and is thus also useful for the treatment of cancer and chronic inflammation. Other exemplified compounds from this series of benzylglycosylamides include the following:



Compound	R1	R2	Formula
290648	H	3-(AcNH)-4-Cl-Ph	C ₃₅ H ₃₇ ClN ₂ O ₁₃
290649	Ac	3-Cl-4-[NC(CH ₂) ₄ O]-Ph	C ₄₆ H ₄₉ ClN ₂ O ₁₇
290651	H	3-Cl-4-[NC(CH ₂) ₄ O]-Ph	C ₃₇ H ₃₉ ClN ₂ O ₁₃
290652	H	3-(AcNH)-4-[NC(CH ₂) ₄ O]-Ph	C ₃₉ H ₄₃ N ₃ O ₁₄
290653	H	3-(AcNH)-4-Cl-PhCH ₂	C ₃₆ H ₃₉ ClN ₂ O ₁₃

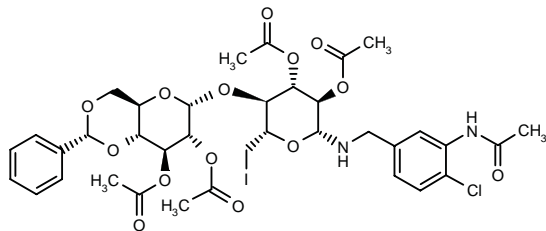
SOURCE – American Home Products.

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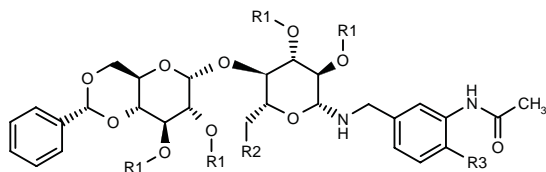
290654

N-[2-Chloro-5-[(*R*)-2,2',3,3'-tetra-*O*-acetyl-4',6'-*O*-benzylidene-6-deoxy- β -D-maltosyloxymethyl]phenyl]-acetamide



C₃₆ H₄₂ Cl I N₂ O₁₄; Mol wt: 889.0808

ACTION – An inhibitor of smooth muscle cell proliferation (IC_{50} = 0.20 μ M using porcine smooth muscle cells), potentially useful for the treatment of diseases caused by excessive smooth muscle cell proliferation such as restenosis. Compound is also reported to inhibit angiogenesis and is thus also useful for the treatment of cancer and chronic inflammation. Other exemplified compounds from this series of benzylmaltosides include the following:



Compound	R1	R2	R3	Formula
290655	H	4-NO ₂ -1-imidazolyl	Me	C ₃₂ H ₃₉ N ₅ O ₁₂
290656	Ac	4-NO ₂ -1-imidazolyl	Cl	C ₃₉ H ₄₄ ClN ₅ O ₁₆
290657	H	4-NO ₂ -1-imidazolyl	Cl	C ₃₁ H ₃₆ ClN ₅ O ₁₂
290658	H	I	Cl	C ₂₈ H ₃₄ ClIN ₂ O ₁₀
290659	Ac	1,3-dioxo-2-isindoliny	Cl	C ₄₄ H ₄₆ ClN ₃ O ₁₆
290660	H	1,3-dioxo-2-isindoliny	Cl	C ₃₆ H ₃₈ ClN ₃ O ₁₂
290661	H	N3	Cl	C ₂₈ H ₃₄ ClN ₅ O ₁₀

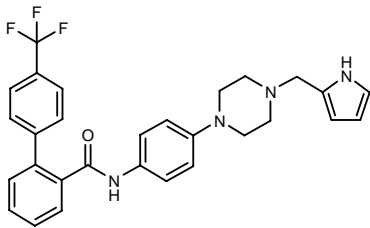
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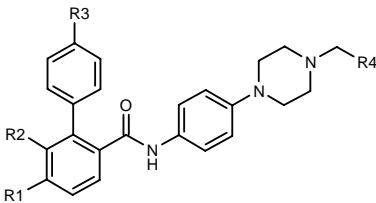
290771

N-[4-[4-(1*H*-Pyrrol-2-ylmethyl)piperazin-1-yl]phenyl]-4'-(trifluoromethyl)biphenyl-2-carboxamide



C29 H27 F3 N4 O; Mol wt: 504.5533

ACTION – Potent and specific inhibitor of the hepatic production of apolipoprotein B-100 (apoB-100; IC₅₀ = 10 nM in primary human hepatocytes) with potential in the treatment of conditions resulting from elevated circulating levels of apoB-100 such as atherosclerosis, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, pancreatitis, non-insulin-dependent diabetes mellitus and coronary heart disease. Other exemplified compounds from this series of benzamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
290772	H	H	CF3	3-CN-Ph	C ₃₂ H ₂₇ F ₃ N ₄ O
290773	Me	H	i-Pr	3-CN-Ph	C ₃₅ H ₃₆ N ₄ O
290774	H	OMe	i-Pr	3-CN-Ph	C ₃₅ H ₃₆ N ₄ O ₂
290775	H	Me	i-Pr	3-CN-Ph	C ₃₅ H ₃₆ N ₄ O
290776	H	Me	CF3	3-CN-Ph	C ₃₃ H ₂₉ F ₃ N ₄ O
290777	Me	H	i-Pr	3-(3-Me-1,2,4-oxadiazol-5-yl)-Ph	C ₃₇ H ₃₉ N ₅ O ₂
290778	Me	H	i-Pr	2-pyrrolyl	C ₃₂ H ₃₆ N ₄ O
290779	Me	H	CF3	2-pyrrolyl	C ₃₀ H ₂₉ F ₃ N ₄ O

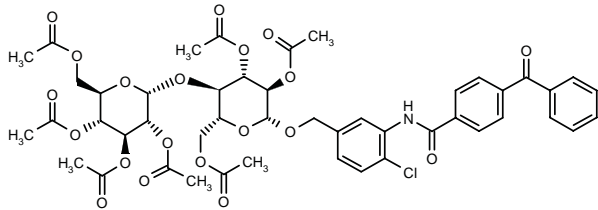
SOURCE – Glaxo Wellcome.

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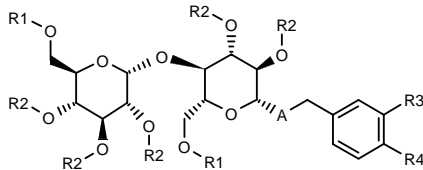
291105

N-[5-(Hepta-*O*-acetyl-β-*D*-maltosyloxymethyl)-2-chlorophenyl]-4-benzoylbenzamide

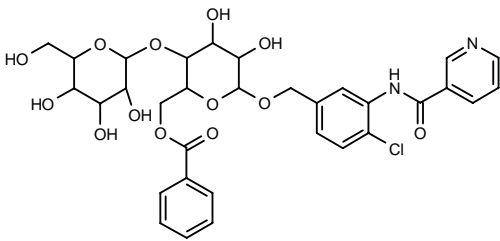


C47 H50 Cl N O20; Mol wt: 984.3520

ACTION – Smooth muscle cell proliferation inhibitor (IC₅₀ = 0.164 μM for inhibition of porcine smooth muscle cell proliferation), potentially useful for the treatment of hyperproliferative vascular disorders, particularly restenosis. Other exemplified acylated benzylmaltosides include the following:



Compound	R1	R2	R3	R4	A	Formula
291106	Ac	Ac	NO2	Cl	O	C ₃₃ H ₄₀ ClNO ₂₀
291107	Ac	Ac	NH2	Cl	S	C ₃₃ H ₄₂ ClNO ₁₇ S
291108	COPh	Ac	NHAc	Cl	O	C ₄₅ H ₄₈ ClNO ₁₉
291110	4-Me-PhSO2	H	NO2	Me	O	C ₃₄ H ₄₁ NO ₁₇ S ₂



291109: C32 H35 Cl N2 O13

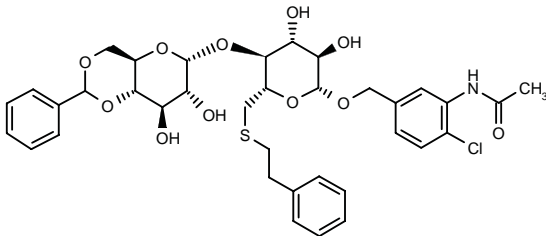
SOURCE – American Home Products.

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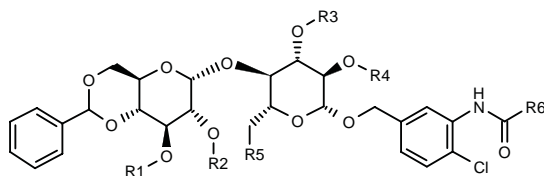
291111

N-[5-[4',6'-*O*-Benzylidene-6-deoxy-6-(2-phenylethylsulfanyl)-β-*D*-maltosyloxymethyl]-2-chlorophenyl]-acetamide



C36 H42 Cl N O11 S; Mol wt: 732.2428

ACTION – Smooth muscle cell proliferation inhibitor ($IC_{50} = 0.005 \mu M$ for inhibition of porcine smooth muscle cell proliferation), potentially useful for the treatment of hyperproliferative vascular disorders, particularly restenosis. Other exemplified 4',6'-acetalbenzylmalto-sides include the following:



Compound	R1=R2=R3=R4	R5	R6	Formula
291112	Ac	SCH2Ph	Me	C ₄₃ H ₄₈ ClNO ₁₅ S
291113	H	SCH2Ph	Me	C ₃₅ H ₄₀ ClNO ₁₁ S
291114	H	2,4-(Cl)2-PhCH2S	Me	C ₃₅ H ₃₈ Cl ₃ NO ₁₁ S
291115	H	SOCH2Ph	Me	C ₃₅ H ₄₀ ClNO ₁₂ S
291116	H	SOCH2Ph	Me	C ₃₅ H ₄₀ ClNO ₁₂ S
291117	Ac	SOCH2Ph	Me	C ₄₃ H ₄₈ ClNO ₁₆ S
291118	H	NHCOPh	Me	C ₃₅ H ₃₈ ClN ₂ O ₁₂
291119	H	SOCH2Ph	OMe	C ₃₅ H ₄₀ ClNO ₁₃ S

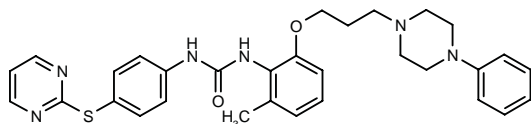
SOURCE – American Home Products.

REFERENCES

1. Dollings, P.J. (American Home Products Corp.) *Acetal benzylmalto-sides as inhibitors of smooth muscle cell proliferation*. WO 0034338.

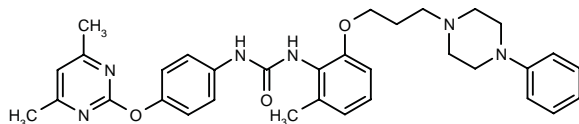
291128

N-[2-Methyl-6-[3-(4-phenylpiperazin-1-yl)propoxy]phenyl]-*N'*-[4-(2-pyrimidinylsulfanyl)phenyl]urea



C31 H34 N6 O2 S; Mol wt: 554.7156

ACTION – Hypolipidemic and antiarteriosclerotic agent with ACAT- and macrophage foaming-inhibitory activity. *In vitro*, compound inhibited ACAT from murine foamed macrophages with an IC_{50} value of $0.0198 \mu M$. Another exemplified compound from this series of diphenylurea derivatives is:



291129: C33 H38 N6 O3

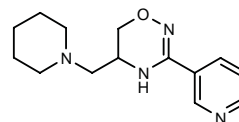
SOURCE – Mitsubishi-Tokyo Pharmaceuticals.

REFERENCES

1. Inoue, N. et al. (Mitsubishi Chemical Corp.) *Diphenylurea derivs*. JP 2000143629.

291497

(-)-5-(1-Piperidinylmethyl)-3-(3-pyridinyl)-5,6-dihydro-4*H*-1,2,4-oxadiazine



C14 H20 N4 O; Mol wt: 260.3390

ACTION – (-)-Enantiomer of a pyridyl-4*H*-1,2,4-oxadiazine compound previously known in racemate form with a distinct pharmacological profile; in particular, compound has substantially stronger vasoprotective and cardioprotective effects than the racemate and the (+)-isomer and was found to exhibit a positive inotropic effect in rabbit papillary muscle at concentrations of 1-100 μM , contrary to the racemate and (+)-enantiomer which exhibited negative inotropic effects. *In vitro*, it was shown to preserve endothelial function in rat hearts subjected to global ischemia at a concentration of 1 μM , in contrast to the racemate and (+)-enantiomer. In addition, when tested *in vivo* in spontaneously hypertensive rats subjected to left coronary artery occlusion, it significantly reduced myocardial infarct size and increased survival rate at 100 mg/kg p.o. given 6 h before occlusion, in contrast with the (+)-enantiomer and the racemate. Claimed for the treatment or prevention of vascular diseases and diseases connected to vascular abnormalities, particularly in patients with cardiac failure.

SOURCE – Biorex R&D.

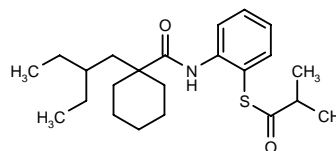
REFERENCES

1. Jednákovits, A. et al. (Biorex Kutató és Fejlesztő Rt.) *Optically active pyridyl-4H-1,2,4-oxadiazine deriv. and its use in the treatment of vascular diseases*. WO 0035914.

JTT-705

291317

2-Methylpropanethioic acid *S*-[2-[1-(2-ethylbutyl)cyclohexylcarboxamido]phenyl] ester



C23 H35 N O2 S; Mol wt: 389.6005

ACTION – Cholesteryl ester transfer protein (CETP) inhibitor (IC₅₀ = 9 μM in human plasma) proven to produce 95% inhibition of the enzyme in rabbits at a dose of 30 mg/kg p.o. After 7-day repeated administration at 0.6% in the diet, a significant increase in plasma HDL cholesterol was seen. In the cholesterol-fed rabbit model of atherosclerosis, treatment with compound at 0.75% in the diet for 6 months resulted in sustained inhibition of CETP activity, a 90% increase in HDL cholesterol levels and a 40-50% decrease in non-HDL cholesterol levels; in comparison, simvastatin (0.0075%) more markedly decreased non-HDL cholesterol (50-70%) but only slightly increased HDL cholesterol (28%). Both treatments produced a similar decrease in atherosclerotic lesion size in the aortic arch (70% for compound vs. 80% for simvastatin). No toxicity was seen in rabbits treated with JTT-705. In a clinical study, compound given at doses of 600-900 mg/day for 14 days produced a 40-45% increase in HDL cholesterol and a 15-20% decrease in LDL cholesterol. JTT-502 is currently undergoing clinical evaluation for the treatment of atherosclerosis.

SOURCE – Japan Tobacco.

REFERENCES

1. Shinkai, H. et al. (Japan Tobacco Inc.) *CEPT activity inhibitors*. EP 1020439, JP 1999049743, JP 1999222428, WO 9835937.

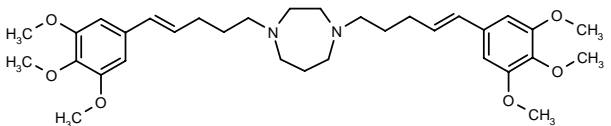
2. Okamoto, H. et al. *A cholesteryl ester transfer protein inhibitor attenuates atherosclerosis in rabbits*. Nature 2000, 406(6792): 203.

3. Shinkai, H. et al. *Bis(2-(acylamino)phenyl) disulfides, 2-(acylamino)benzenethiols, and S-(2-(acylamino)phenyl) alkanethioates as novel inhibitors of cholesteryl ester transfer protein*. J Med Chem 2000, 43(19): 3566.

K-7174

291665

1,4-Bis[5-(3,4,5-trimethoxyphenyl)-4(*E*)-pentenyl]hexa-hydro-1*H*-1,4-diazepine



C33 H48 N2 O6; Mol wt: 568.7502

ACTION – Cell adhesion inhibitor proven to inhibit the expression of VCAM-1 in human umbilical vein endothelial cells (HUVEC) induced by either TNF-α or IL-1β (IC₅₀ = 14 μM), without affecting the induction of ICAM-1 or E-selectin expression. The mechanism by which compound inhibited cell adhesion appeared to be via regulation of the binding activity of the GATA motif to the VCAM-1 gene. Potentially useful for the treatment of atherosclerosis and other inflammatory disorders.

SOURCE – Kowa.

REFERENCES

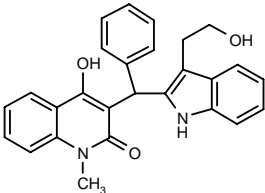
1. Nakao, H. et al. (Kowa Co., Ltd.) *Cell adhesion inhibitor*. EP 0774257, JP 1997143075, US 5723465.

2. Umetani, M. et al. *A novel cell adhesion inhibitor, K-7174, reduces the endothelial VCAM-1 induction by inflammatory cytokines, acting through the regulation of GATA*. Biochem Biophys Res Commun 2000, 272(2): 370.

SF-2809-VI

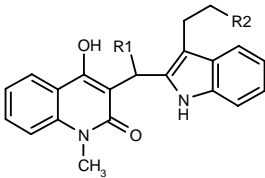
290901

4-Hydroxy-3-[1-[3-(2-hydroxyethyl)-1*H*-indol-2-yl]-1-phenylmethyl]-1-methylquinolin-2(1*H*)-one



C27 H24 N2 O3; Mol wt: 424.4976

ACTION – Compound isolated from the bacterial strain SF2809 (FERM BP-6872) that exhibits chymase-inhibitory activity (IC₅₀ = 0.014 μM in an *in vitro* assay using human enzyme) and is therefore expected to be useful for the treatment of myocardial infarction, cardiac hypertrophy, heart failure, arteriosclerosis, hypertension, allergic and antiinflammatory diseases, etc. Other compounds from the same source are:



Compound	R1	R2	Formula
SF-2809-I [290902]	H	NHAc	C ₂₃ H ₂₃ N ₃ O ₃
SF-2809-V [290903]	Ph	NHAc	C ₂₉ H ₂₇ N ₃ O ₃
SF-2809-III [290904]	H	OH	C ₂₁ H ₂₀ N ₂ O ₃
SF-2809-IV [290905]	4-OH-Ph	OH	C ₂₇ H ₂₄ N ₂ O ₄

SOURCES – Meiji Seika; Teijin.

REFERENCES

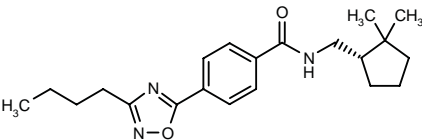
1. Tani, M. et al. (Meiji Seika Kaisha, Ltd.;Teijin Ltd.) *SF2809-I, II, III, IV, V and VI substances exhibiting chymase-inhibiting activities*. WO 0032587.

ANTIARRHYTHMIC DRUGS

BMS-208782

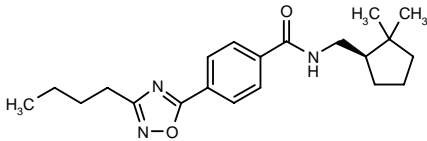
292590

(*S*)-4-(3-Butyl-1,2,4-oxadiazol-5-yl)-*N*-(2,2-dimethylcyclopentylmethyl)benzamide



C21 H29 N3 O2; Mol wt: 355.4791

ACTION – Potent, orally available potassium current $K_{V(s)}$ (IK_s) blocker with high selectivity relative to other potassium, sodium and calcium ion currents. Potentially useful for the prevention of cardiac arrhythmias.



BMS-208783 [292591]: C21 H29 N3 O2

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Lloyd, J. et al. (Bristol-Myers Squibb Co.) *Benzoic acid derivs. and related cpds. as antiarrhythmic agents*. WO 9837068.

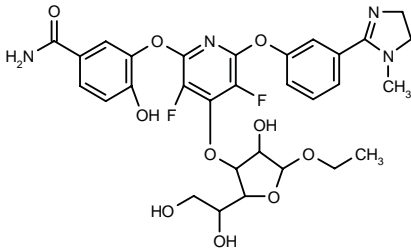
2. Lloyd, J. et al. *Design and synthesis of potent, selective, and orally bioavailable potassium (IK_s) blockers*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 327.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

290676

3-[4-[2-(1,2-Dihydroxyethyl)-5-ethoxy-4-hydroxy-tetrahydrofuran-3-yloxy]-3,5-difluoro-6-[3-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)phenoxy]pyridin-2-yloxy]-4-hydroxybenzamide



C30 H32 F2 N4 O10; Mol wt: 646.5968

ACTION – Anticoagulant and antithrombotic agent, a specifically claimed compound from a series of polyhydroxylated heterocyclic anticoagulants with human factor Xa-inhibitory activity.

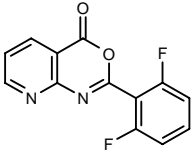
SOURCE – Berlex.

REFERENCES

1. Phillips, G.B. (Berlex Laboratories, Inc.) *Polyhydroxylated heterocyclic derivs. as anti-coagulants*. WO 0031068.

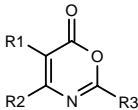
290692

2-(2,6-Difluorophenyl)-4H-pyrido[2,3-d][1,3]oxazin-4-one



C13 H6 F2 N2 O2; Mol wt: 260.1984

ACTION – Anticoagulant that acts by inhibiting tissue factor/factor VIIa (TF/FVIIa) activity. *In vitro*, compound was shown to inhibit TF/FVIIa-catalyzed activation of factor X, as well as TF/FVIIa-induced clotting of human plasma. Other exemplified heterocyclic compounds include the following:



Compound	R1	R2	R3	Formula
290693	-C(2-thienyl)=CHS-		2-furyl	C ₁₄ H ₇ NO ₃ S ₂
290695	-C(Me)=CHS-		2-NO ₂ -Ph	C ₁₃ H ₈ N ₂ O ₄ S
290696	-SCH=C(Me)-		2,6-(F)2-Ph	C ₁₃ H ₇ F ₂ NO ₂ S
290698	-CH=NN(Me)-		2-Me-Ph	C ₁₃ H ₁₁ N ₃ O ₂
290700	-CH=NC(EtS)=N-		2-Me-Ph	C ₁₅ H ₁₃ N ₃ O ₂ S
290701	-CH=CHCH=N-		2-F-Ph	C ₁₃ H ₇ FN ₂ O ₂
290703	-CH=CHN=CH-		2,6-(F)2-Ph	C ₁₃ H ₆ F ₂ N ₂ O ₂

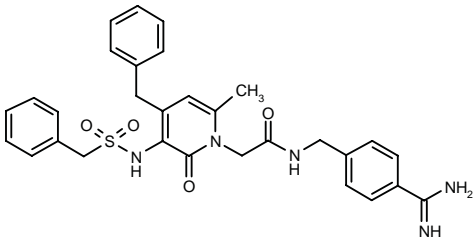
SOURCE – Novo Nordisk.

REFERENCES

1. Jakobsen, P. et al. (Novo Nordisk A/S) *Heterocyclic cpds. regulating clotting*. WO 0030646.

290787

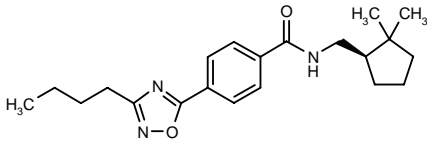
N-(4-Amidinobenzyl)-2-[4-benzyl-3-(benzylsulfonamido)-6-methyl-2-oxo-1,2-dihydropyridin-1-yl]acetamide



C30 H31 N5 O4 S; Mol wt: 557.6719

ACTION – Antithrombotic agent that inhibits human thrombin and exhibits an anticoagulant effect in rat plasma *ex vivo*. Other specifically claimed 2-pyridone derivatives include the following:

ACTION – Potent, orally available potassium current $K_{V(s)}$ (IK_s) blocker with high selectivity relative to other potassium, sodium and calcium ion currents. Potentially useful for the prevention of cardiac arrhythmias.



BMS-208783 [292591]: C21 H29 N3 O2

SOURCE – Bristol-Myers Squibb.

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1. Lloyd, J. et al. (Bristol-Myers Squibb Co.) *Benzoic acid derivs. and related cpds. as antiarrhythmic agents*. WO 9837068.

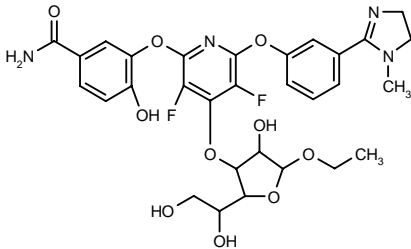
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AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

290676

3-[4-[2-(1,2-Dihydroxyethyl)-5-ethoxy-4-hydroxy-tetrahydrofuran-3-yloxy]-3,5-difluoro-6-[3-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl)phenoxy]pyridin-2-yloxy]-4-hydroxybenzamide



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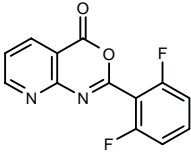
SOURCE – Berlex.

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1. Phillips, G.B. (Berlex Laboratories, Inc.) *Polyhydroxylated heterocyclic derivs. as anti-coagulants*. WO 0031068.

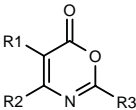
290692

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290695	-C(Me)=CHS-		2-NO ₂ -Ph	C ₁₃ H ₈ N ₂ O ₄ S
290696	-SCH=C(Me)-		2,6-(F)2-Ph	C ₁₃ H ₇ F ₂ NO ₂ S
290698	-CH=NN(Me)-		2-Me-Ph	C ₁₃ H ₁₁ N ₃ O ₂
290700	-CH=NC(EtS)=N-		2-Me-Ph	C ₁₅ H ₁₃ N ₃ O ₂ S
290701	-CH=CHCH=N-		2-F-Ph	C ₁₃ H ₇ FN ₂ O ₂
290703	-CH=CHN=CH-		2,6-(F)2-Ph	C ₁₃ H ₆ F ₂ N ₂ O ₂

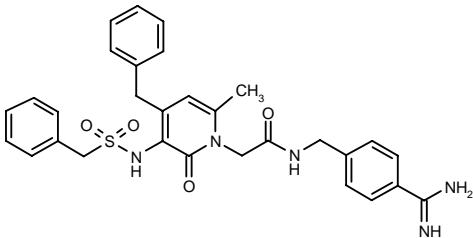
SOURCE – Novo Nordisk.

REFERENCES

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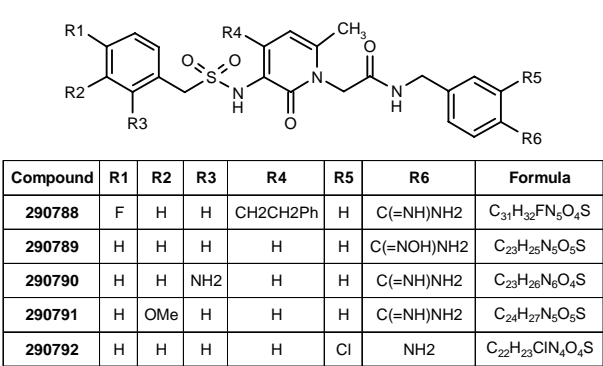
290787

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ACTION – Antithrombotic agent that inhibits human thrombin and exhibits an anticoagulant effect in rat plasma *ex vivo*. Other specifically claimed 2-pyridone derivatives include the following:



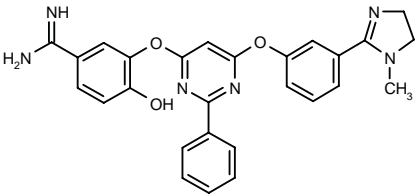
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Lassalle, G. et al. (Sanofi-Synthélabo) *Novel 2-pyridone derivs., preparation method and therapeutic use.* FR 2786482, WO 0032574.

291073

4-Hydroxy-3-[6-[3-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl)phenoxy]-2-phenylpyrimidin-4-yloxy]benzamidine



C27 H24 N6 O3; Mol wt: 480.5256

ACTION – Anticoagulant, a factor Xa inhibitor. A representative compound from a series of aryl and heteroaryl substituted pyrimidine derivatives.

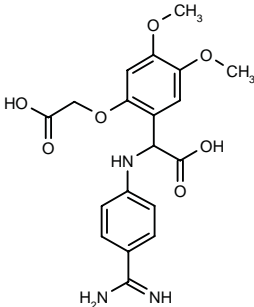
SOURCE – Berlex.

REFERENCES

1. Davey, D.D. and Phillips, G.B. (Berlex Laboratories, Inc.) *Aryl and heterocyclyl subst. pyrimidine derivs. as anticoagulants.* US 6127376, WO 0033844.

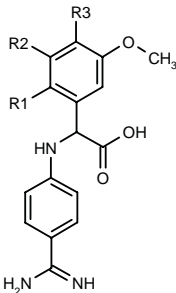
291525

2-(4-Amidinophenylamino)-2-[2-(carboxymethoxy)-4,5-dimethoxyphenyl]acetic acid



C19 H21 N3 O7; Mol wt: 403.3889

ACTION – Antithrombotic agent that inhibits the formation of coagulation factors Xa, IXa and thrombin induced by factor VIIa and tissue factor. The compound inhibits the amidolytic activity of the factor VIIa/tissue factor complex, as demonstrated in a chromogenic assay ($K_i = 0.0385 \mu\text{M}$). Potentially useful for the treatment or prevention of thrombosis, stroke, myocardial infarction, inflammation and arteriosclerosis or as an antitumor agent. Other exemplified phenylglycine derivatives are:



Compound	R1	R2	R3	Formula
291526	H	H	OCH2Ph	C ₂₃ H ₂₃ N ₃ O ₄
291527	OCH2CO2H	OMe	H	C ₁₉ H ₂₁ N ₃ O ₇

SOURCE – Roche.

REFERENCES

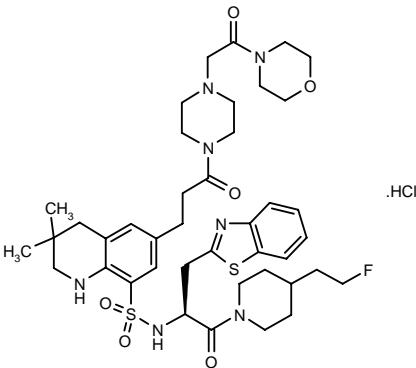
1. Ackermann, J. et al. (F. Hoffmann-La Roche AG) *Phenylglycine derivs.* WO 0035858.

CGH-1484A

292051

N-[1(*S*)-(Benzothiazol-2-ylmethyl)-2-[4-(2-fluoroethyl)piperidin-1-yl]-2-oxoethyl]-3,3-dimethyl-6-[3-[4-[2-(4-morpholinyl)-2-oxoethyl]piperazin-1-yl]-3-oxopropyl]-1,2,3,4-tetrahydroquinoline-8-sulfonamide hydrochloride

(*S*)-4-[2-[4-[3-[8-[1-(2-Benzothiazolylmethyl)-2-[4-(2-fluoroethyl)-1-piperidinyl]-2-oxoethylaminosulfonyl]-1,2,3,4-tetrahydro-3,3-dimethyl-6-quinolinyl]-1-oxopropyl]-1-piperazinyl]acetyl]morpholine hydrochloride



C41 H56 F N7 O6 S2 . HCl; Mol wt: 862.5273

ACTION – Anticoagulant, an orally active thrombin inhibitor ($K_i = 57$ nM) with high selectivity over trypsin, chymotrypsin, plasmin and factor Xa ($K_i = 153, 12.2, 212$ and > 2000 μ M, respectively). Compound showed improved water solubility (0.13 mg/ml at pH 7 and 15 mg/ml at pH 2) and oral bioavailability (28% in rats) compared to its parent compound CGH-752, and it significantly inhibited platelet deposition in an acute injury-induced model of thrombus formation in the rat dorsal aorta (60% inhibition at 10 or 20 mg/kg p.o.).

SOURCE – Novartis.

REFERENCES

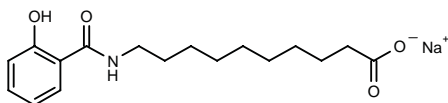
1. Brundish, D.E. et al. (Novartis AG) *Tetrahydroquinoline inhibitors of trypsin and thrombin*. GB 2312674.

2. Hayler, J. et al. *The design and synthesis of thrombin inhibitors: The introduction of in vivo efficacy and oral bioavailability into benzthiazolylalanine inhibitors*. Bioorg Med Chem Lett 2000, 10(14): 1567.

SNAD¹⁻⁷

292042

10-(2-Hydroxybenzamido)decanoic acid sodium salt



C17 H24 N Na O4; Mol wt: 329.3696

ACTION – Delivery agent that facilitates the gastrointestinal absorption of low-molecular-weight heparin (LMWH) by forming a noncovalent interaction that allows the complex to pass through the gastrointestinal mucosa. In a porcine model of deep vein thrombosis, 7-day enteral administration of the combination significantly decreased the caval thrombus weight and increased plasma levels of anti-factor Xa. In a similar study in jugular vein thrombosis in rats, the combination given orally (15 mg/kg LMWH and 300 mg/kg SNAD) was able to significantly prevent deep vein thrombosis and to increase serum levels of anti-factor Xa. Potentially useful in combination with LMWH for the prevention of deep vein thrombosis.

Oral formulation of the low-molecular-weight heparin (LMWH) enoxaparin using the complexing agent delivery system (CADDYS) carrier SNAD

SNAD/LMWH [292192]^{4,6,7}

SOURCE – Emisphere.

REFERENCES

1. Leone-Bay, A. (Emisphere Technologies, Inc.) *Cpds. and compsns. for delivering active agents*. WO 9736480.

2. Leone-Bay, A. et al. (Emisphere Technologies, Inc.) *Cpds. and compsns. for delivering active agents*. US 5650386, WO 9630036.

3. Leone-Bay, A. et al. (Emisphere Technologies, Inc.) *Cpds. and compsns. for delivering active agents*. US 5866536.

4. Leone-Bay, A. et al. *Studies evaluating the efficacy of orally-delivered low molecular weight heparin in rats*. Proc Int Symp Control Release Bioact Mater 1999, 26: 976.

5. Leone-Bay, A. et al. *Synthesis and evaluation of compounds that facilitate the gastrointestinal absorption of heparin*. J Med Chem 1998, 41(7): 1163.

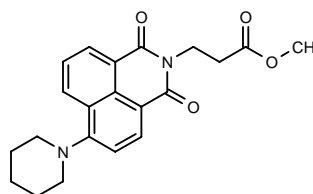
6. Salartash, K. et al. *Oral low-molecular weight heparin and delivery agent prevents jugular venous thrombosis in the rat*. J Vasc Surg 1999, 30(3): 526.

7. Salartash, K. et al. *Treatment of experimentally induced caval thrombosis with oral low molecular weight heparin and delivery agent in a porcine model of deep venous thrombosis*. Ann Surg 2000, 231(6): 789.

ANTIPLATELET THERAPY

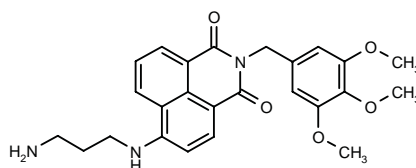
290679

3-[1,3-Dioxo-6-(1-piperidiny)-2,3-dihydro-1 *H*-benzo[*de*]-isoquinolin-2-yl]propionic acid methyl ester



C21 H22 N2 O4; Mol wt: 366.4148

ACTION – Glycoprotein IbIX antagonist with potential for the treatment or prevention of thrombotic disorders including acute coronary syndrome, angina pectoris, myocardial infarction, peripheral circulatory disorders, stroke, transient ischemic attacks, arteriosclerosis and restenosis following angioplasty. Another specifically claimed compound from this series of substituted benzo[*de*]isoquinoline-1,3-diones is:



290680: C25 H27 N3 O5

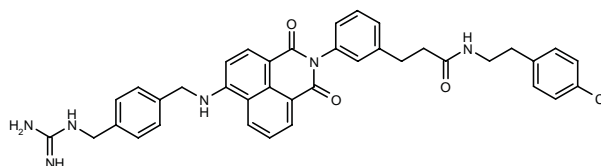
SOURCE – Merck KGaA.

REFERENCES

1. Mederski, W. et al. (Merck Patent GmbH) *Substd. benzo[de]isoquinoline-1,3-diones*. WO 0031039.

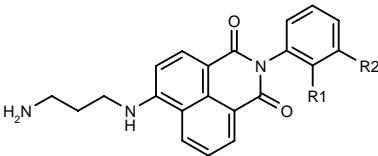
290759

N-[2-(4-Chlorophenyl)ethyl]-3-[3-[6-[4-(guanidinomethyl)-benzylamino]-1,3-dioxo-2,3-dihydro-1 *H*-benzo[*de*]-isoquinolin-2-yl]phenyl]propionamide

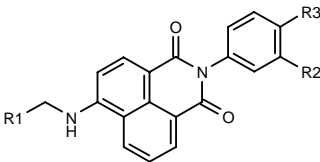


C38 H35 Cl N6 O3; Mol wt: 659.1865

ACTION – Glycoprotein IbIX antagonist for the treatment or prevention of thrombotic disorders including acute coronary syndrome, angina pectoris, myocardial infarction, peripheral circulatory disorders, stroke, transient ischemic attacks, arteriosclerosis and restenosis following angioplasty. Other specifically claimed substituted benzo[*de*]isoquinoline-1,3-diones include the following:



Compound	R1	R2	Formula
290760	-CH=C(OH)CH=CH-		C ₂₅ H ₂₁ N ₃ O ₃
290761	OMe	OMe	C ₂₃ H ₂₃ N ₃ O ₄



Compound	R1	R2	R3	Formula
290762	4-(NH ₂ C(=NH)NH-CH ₂)-cyclohexyl	4-Cl-PhCH ₂ CH ₂ -NHCOCH ₂ CH ₂	H	C ₃₈ H ₄₁ ClN ₆ O ₃
290763	CH ₂ CH ₂ NH ₂	H	9-carbazoyl	C ₃₃ H ₂₆ N ₄ O ₂
290764	3-[CH ₂ NH-C(=NH)NH ₂]-Ph	H	4-MeO-Ph	C ₃₄ H ₂₉ N ₅ O ₃
290765	CH ₂ NHC(=NH)NH ₂	4-Cl-PhCH ₂ CH ₂ -NHCOCH ₂ CH ₂	H	C ₃₂ H ₃₁ ClN ₆ O ₃
290766	CH ₂ CH ₂ N(Me)-(CH ₂) ₃ NHC(=NH)NH ₂	4-Cl-PhCH ₂ CH ₂ -NHCOCH ₂ CH ₂	H	C ₃₇ H ₄₂ ClN ₇ O ₃
290768	CH ₂ CH ₂ NH ₂	H	4-MeO-Ph	C ₂₈ H ₂₈ N ₃ O ₃

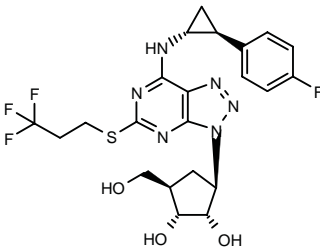
SOURCE – Merck KGaA.

REFERENCES

1. Mederski, W. et al. (Merck Patent GmbH) *Substd. benzo[de]isoquinoline-1,3-diones*. WO 0032577.

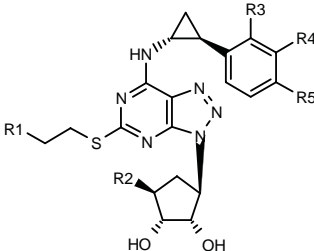
291227

3(*R*)-[7-[*trans*-2-(4-Fluorophenyl)cyclopropylamino]-5-(3,3,3-trifluoropropylsulfanyl)-3-*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5(*R*)-(hydroxymethyl)cyclopentane-1(*R*),2(*S*)-diol



C22 H24 F4 N6 O3 S; Mol wt: 528.5286

ACTION – P2T receptor antagonist that inhibits ADP-induced platelet aggregation and is useful for the treatment or prevention of arterial thrombosis-related conditions such as myocardial infarction, thrombotic stroke, transient ischemic attacks, peripheral vascular disease and angina. Other specifically claimed triazolo-[4,5-*d*]pyrimidine derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
291228	CF ₃	OCH ₂ CH ₂ OH	F	H	F	C ₂₃ H ₂₅ F ₅ N ₆ O ₄ S
291229	Me	CH ₂ OH	F	H	F	C ₂₂ H ₂₆ F ₂ N ₆ O ₃ S
291230	Et	CH ₂ OH	F	H	F	C ₂₃ H ₂₈ F ₂ N ₆ O ₃ S
291231	Et	OH	H	H	F	C ₂₂ H ₂₇ FN ₆ O ₃ S
291232	CF ₃	OCH ₂ CH ₂ OH	H	F	F	C ₂₃ H ₂₅ F ₅ N ₆ O ₄ S
291233	CF ₃	OCH ₂ CH ₂ OH	H	H	H	C ₂₃ H ₂₇ F ₃ N ₆ O ₄ S
291234	Et	OH	H	F	F	C ₂₂ H ₂₆ F ₂ N ₆ O ₃ S
291235	Et	OCH ₂ CH ₂ OH	H	H	H	C ₂₄ H ₃₂ N ₆ O ₄ S

SOURCE – AstraZeneca.

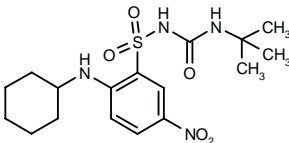
REFERENCES

1. Guile, S. et al. (AstraZeneca U.K., Ltd.;AstraZeneca AB) *Novel triazolo(4,5-d)pyrimidine cpds*. WO 0034283.

BM-531

291666

N-*tert*-Butyl-*N*'-(2-cyclohexylamino-5-nitrobenzene-sulfonyl)urea



C17 H26 N4 O5 S; Mol wt: 398.4814

ACTION – TxA₂ receptor antagonist with high affinity for TxA₂ receptors on human washed platelets (IC₅₀ = 7.8 nM), superior to that of torasemide, SQ-29548, sulotroban and BM-500 (IC₅₀ = 2.69, 0.021, 0.93 and 0.079 μM, respectively). Compound prevented aggregation of human platelet-rich plasma induced by arachidonic acid (ED₁₀₀ = 0.125 μM), U-46619 (ED₅₀ = 0.482 μM) and collagen (42.9% inhibition at 10 μM).

SOURCES – University of Liège, Liège (BE); University of Namur, Namur (BE).

REFERENCES

1. Dogné, J.-M. et al. *Effects of a novel non-carboxylic thromboxane A₂ receptor antagonist (BM-531) derived from torasemide on platelet function*. Prostaglandins Leukot Essent Fatty Acids 2000, 62(5): 311.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

FIDUXOSIN HYDROCHLORIDE*

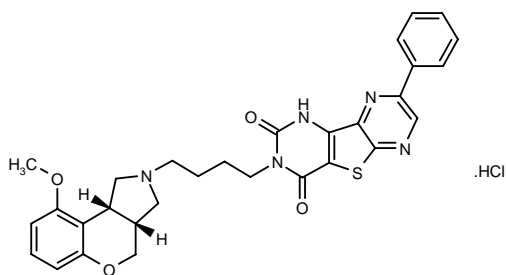
Prop INN; USAN

267561

(3a*R*,9b*R*)-*cis*-3-[4-(9-Methoxy-1,2,3,3a,4,9b-hexahydro-[1]benzopyrano[3,4-*c*]pyrrol-2-yl)butyl]-8-phenylpyrazino[2',3':4,5]thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione hydrochloride

ABT-980

A-185980.1



C30 H29 N5 O4 S . HCl; Mol wt: 592.1170

ACTION – Potent, uroselective $\alpha_{1A/1D}$ -adrenoceptor antagonist ($K_i = 0.16$ and 0.92 nM, respectively) with 155-fold selectivity for the α_{1A} versus α_{1B} subtype ($K_i = 5.7$ nM) in radioligand binding studies. In anesthetized dogs, compound blocked the increase in intraurethral pressure induced by epinephrine ($pA_2 = 8.1$), whereas it induced only a transient decrease in mean arterial pressure ($pED_{50} = 5.2$), indicating a marked uroselectivity (770-fold), higher than that of tamsulosin and terazosin (35- and 3-fold, respectively). Compound is in phase II trials as a potential treatment for benign prostatic hyperplasia.

SOURCE – Abbott.

REFERENCES

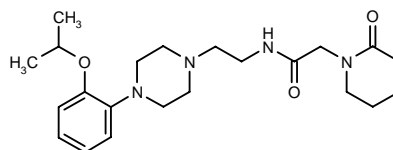
- Meyer, M.D. et al. (Abbott Laboratories Inc.) *Benzopyranopyrrole and benzopyranopyridine α_1 -adrenergic cpds.* EP 0942911, US 5891882, US 6046207, WO 9824791.
- Drizin, I. et al. *Structure activity studies leading to the identification of ABT-980 (fiduxosin): A novel selective α_{1A}/α_{1D} antagonist for the symptomatic treatment of benign prostatic hyperplasia (BPH).* 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 297.
- Hancock, A.A. et al. *Fiduxosin - An $\alpha_{1A/D}$ receptor antagonist with enhanced in vivo uroselectivity relative to terazosin and tamsulosin.* J Urol 2000, 163(4, Suppl.): Abst 1377.
- Meyer, M.D. et al. *Discovery of ABT-980 (fiduxosin): A novel potent and selective α_{1A}/α_{1D} adrenoceptor antagonist for the symptomatic treatment of benign prostatic hyperplasia.* 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 296.
- Proposed international nonproprietary names (Prop. INN): List 82.* WHO Drug Inf 1999, 13(4): 276.
- Abbott Laboratories Annual Report 1999.

*Identified compound **267561** (see **266227**) Drug Data Rep 1998, 020(09): 0777.

RWJ-38063*

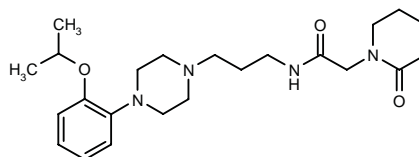
271338

N-[2-[4-(2-Isopropoxyphenyl)piperazin-1-yl]ethyl]-2-(2-oxopiperidin-1-yl)acetamide



C22 H34 N4 O3; Mol wt: 402.5356

ACTION – Potent α_{1A} -adrenoceptor antagonist with high affinity for α_{1A} over α_{1B} and α_{1D} -adrenoceptors ($pK_i = 8.03$, 5.06 and 6.35 , respectively). Functional studies demonstrated that compound has high tissue selectivity, with 319-fold greater potency in inhibiting prostate tissue contractility over that of aorta ($pK_B = 8.24$ and 5.73 , respectively). In anesthetized dogs, it suppressed the intraurethral pressure response to phenylephrine (at 30 and 300 $\mu\text{g/kg}$ i.v.) to a greater extent than the mean arterial pressure response. Potentially useful for the treatment of benign prostatic hyperplasia (BPH) symptoms. Another uroselective arylpiperazine is:



RWJ-69736 [289882]:** C23 H36 N4 O3

SOURCE – Ortho-McNeil.

REFERENCES

- Jolliffe, L. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Arylsubstd. piperazines useful in the treatment of benign prostatic hyperplasia.* EP 0984777, US 6071915, WO 9851298.
- Li, X. et al. *Novel arylpiperazines as selective α_1 -adrenergic receptor antagonists.* Bioorg Med Chem Lett 2000, 10(10): 1093.
- Pulito, V.L. et al. *An investigation of the uroselective properties of four novel α_{1A} -adrenergic receptor subtype-selective antagonists.* J Pharmacol Exp Ther 2000, 294(1): 224.

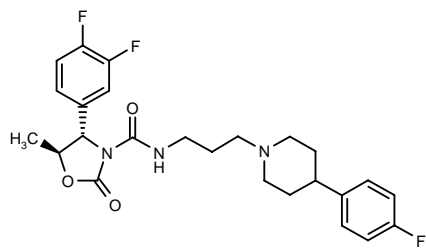
*Identified compound **271338** Drug Data Rep 1999, 021(02): 0139.

Identified compound **289882 Drug Data Rep 2000, 022(08): 0706.

SNAP-7915

291308

(+)-4-(S)-(3,4-Difluorophenyl)-N-[3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl]-5(S)-methyl-2-oxooxazolidine-3-carboxamide



C25 H28 F3 N3 O3; Mol wt: 475.5082

Hydrochloride, m.p. 81-5 °C; [α]_D +27.4° (c 0.47, MeOH).

ACTION – Potent and selective α_{1A}-adrenoceptor antagonist with high binding affinity for recombinant human α_{1A}-over α_{1B}- and α_{1D}-adrenoceptors (K_i = 0.17, 119 and 122 nM, respectively); high binding affinity was also observed for recombinant rat and dog α_{1A}-adrenoceptors (K_i = 0.36 and 0.23 nM, respectively), indicating no significant species differences. However, compound did not exhibit significant binding affinity for rat L-type calcium channels and a number of G-protein-coupled receptors including α₂-adrenoceptors, histamine and 5-HT receptors. In *in vitro* functional experiments, compound was seen to antagonize both A-61603- and phenylephrine-induced contractions of human, dog and rat prostatic tissues (K_i = 0.1-0.33 nM). In anesthetized rats, it showed antagonist activity against the contractile response to phenylephrine in prostate (AD₅₀ = 12 µg/kg i.v.) more potent than terazosin (AD₅₀ = 52 µg/kg i.v.), whereas it was devoid of hypotensive effect in dogs at doses up to 300 µg/kg i.v., in contrast to terazosin which produced hypotension at a dose of 72 µg/kg. Further experiments in dogs demonstrated its ability to block phenylephrine-induced increases in intraurethral pressure at doses significantly lower than those required by terazosin (K_b = 3 and 16 µg/kg i.v., respectively), giving a uroselectivity of at least 100-fold versus only 4-fold for terazosin. Compound showed good oral bioavailability and a long plasma half-life in rats (25% and 6 h, respectively) and dogs (74% and > 12 h, respectively). Potentially useful for the symptomatic relief of benign prostatic hyperplasia (BPH).

SOURCES – Merck & Co; Synaptic.

REFERENCES

1. Broten, T.P. et al. (Merck & Co., Inc.) *Combination therapy for the treatment of benign prostatic hyperplasia*. WO 9948530.

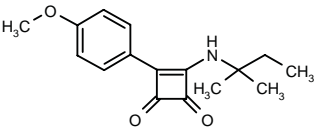
2. Lagu, B. et al. (Synaptic Pharmaceutical Corp.) *Heterocyclic substd. piperidines and uses thereof*. EP 0988295, WO 9857940.

3. Lagu, B. et al. *De novo design of a novel oxazolidinone analogue as a potent and selective α_{1A} adrenergic receptor antagonist with high oral bioavailability*. J Med Chem 2000, 43(15): 2775.

TREATMENT OF URINARY INCONTINENCE

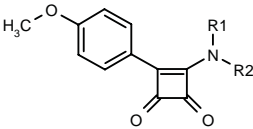
291208

3-(1,1-Dimethylpropylamino)-4-(4-methoxyphenyl)-3-cyclobutene-1,2-dione



C16 H19 N O3; Mol wt: 273.3301

ACTION – Smooth muscle relaxant that acts by activating the large-conductance calcium-sensitive potassium channel (BK_{Ca}) and is selective for bladder tissue, giving IC₅₀ values of 2.5 ± 0.49 and 37.65 ± 6.05 µM, respectively, when tested for smooth muscle relaxant activity in rat bladder and aorta. Particularly useful for the treatment of urinary incontinence and irritable bowel syndrome. Other exemplified aminocyclobuten-3-ene-1,2-diones are:



Compound	R1	R2	Formula
291209	C(Me)2CH2Ph	H	C ₂₁ H ₂₁ NO ₃
291211	i-Pr	Me	C ₁₅ H ₁₇ NO ₃
291214	t-BuCH(Me)	H	C ₁₇ H ₂₁ NO ₃

SOURCE – American Home Products.

REFERENCES

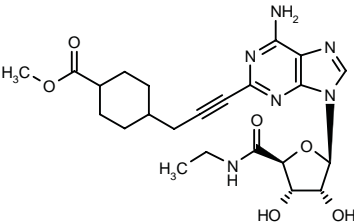
1. Butera, J.A. et al. (American Home Products Corp.) *4-3-Substd.-amino-cyclobut-3-ene-1,2-diones and use for influencing smooth muscle contraction*. WO 0034230.

TREATMENT OF RENAL DISEASES

DWH-146e

282819

4-[3-[6-Amino-9-[(2R,3R,4S,5S)-5-(N-ethylcarbamoyl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-2-yl]-2-propynyl]cyclohexanecarboxylic acid methyl ester



C23 H30 N6 O6; Mol wt: 486.5260

ACTION – Adenosine A_{2A} receptor agonist found to be more potent (72-fold) and more selective than the prototype compound CGS-21680 in binding studies using human receptors. Compound prevented tissue inflammation injury caused by lung transplantation, vascular trauma and renal ischemia–reperfusion in preclinical models in rodents. In addition, it could inhibit inflammation in three models of infection: meningitis, infectious arthritis and sepsis. Studies on the mechanism of action of the compound demonstrated that it inhibits neutrophil adhesion and it may also act by inhibiting TNF-α production by inflammatory cells. Compound may also be useful for vasodilator coronary stress imaging.

SOURCE – University of Virginia, Charlottesville, VA (US).

REFERENCES

1. Fang, G. et al. *DWH146e (DWH), a new selective adenosine A_{2a} receptor agonist, inhibits neutrophil (PMN) recruitment in a murine model of peritonitis*. 37th Annu Meet Infect Dis Soc Am (Nov 18-21, Philadelphia) 1999, Abst 171.

2. Glover, D.K. et al. *Vasodilator stress imaging using new adenosine A_{2A} receptor agonists administered by bolus injection*. J Am Coll Cardiol 2000, 35(2, Suppl. A): Abst 911-1.

3. Hafezi-Moghadam, A. et al. *The adenosine A_{2A} receptor agonist DWH-146e promotes L-selectin shedding and increases leukocyte rolling velocity in vivo*. Exp Biol 2000 (April 15-18, San Diego) 2000, Abst LB159.

4. Linden, J. et al. *Adenosine therapeutics LLC targets agonists of A_{2A} adenosine receptors for coronary imaging and to prevent inflammation injury by transplantation, vascular trauma and ischemia-reperfusion (I/R)*. Drug Dev Res 2000, 50(1): Abst 078.

5. Linden, J. et al. *Agonists of A_{2A} adenosine receptors inhibit endotoxin-induced inflammation and killing*. Drug Dev Res 2000, 50(1): Abst S05-01.

6. Okusa, M.D. et al. *A_{2A}-adenosine receptor mediated inhibition of renal injury and neutrophil adhesion following ischemia reperfusion of kidneys*. Drug Dev Res 2000, 50(1): Abst 021.

7. Okusa, M.D. et al. *Agonists of A_{2A}-adenosine receptors (ARs) are potent inhibitors of activated monocyte/macrophage release of tumor necrosis factor alpha (TNFalpha)*. 32nd Annu Meet Am Soc Nephrol (ASN) (Nov 5-8, Miami Beach) 1999, Abst A2697.

8. Okusa, M.D. et al. *Selective A_{2A} adenosine receptor activation reduces ischemia-reperfusion injury in rat kidney*. Am J Physiol 1999, 277(3, Part 2): F404.

9. Peirce, S.M. et al. *Attenuation of I/R injury in skin using a selective A_{2A} adenosine receptor agonist*. FASEB J 2000, 14(4): Abst 333.1.

10. Ross, S.D. et al. *Selective adenosine-A_{2A} activation reduces lung reperfusion injury following transplantation*. J Heart Lung Transplant 1999, 18(10): 994.

ISIS-24195

291063

18-Mer chimeric phosphorothioate oligonucleotide whose sequence is: GGGCGAGTGAGGAAAGGA, in which the central ten nucleosides are 2'-deoxynucleosides, the four nucleosides flanking the 5'- and 3'-ends are 2'-O-(2-methoxyethyl)-substituted nucleosides and the cytidine in position 4 is 2'-O-(2-methoxyethyl)-5-methylcytidine

ACTION – Antisense chimeric phosphorothioate oligonucleotide targeted to nucleic acids encoding human EGR-1 (early growth response-1, also known as Krox-24, sif/268, NGFI-A, cef5 and GOS30), a transcriptional activator protein that plays a major role in the regulation of signaling cascades in the immune system and apoptosis. Potentially useful for modulating the expression of this protein and thus for the treatment of conditions associated therewith, particularly inflammatory conditions, vascular occlusive lesions and mesangioproliferative glomerulonephritis. *In vitro*, compound inhibited EGR-1 mRNA levels in human cells by 75% at 150 nM.

SOURCE – Isis Pharmaceuticals.

REFERENCES

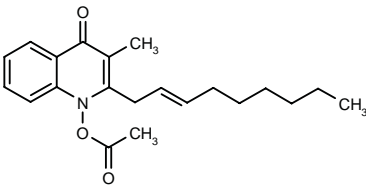
1. Monia, B.P. and Cowsert, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of EGR-1 expression*. WO 0034302.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

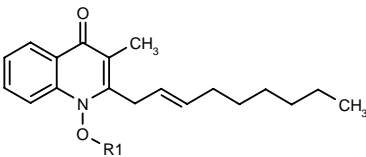
291134

1-Acetoxy-3-methyl-2-[2(E)-nonenyl]quinolin-4(1H)-one



C21 H27 N O3; Mol wt: 341.4483

ACTION – Anti-*Helicobacter pylori* agent from a series of quinolone derivatives wherein the following are also included:



Compound	R1	Formula
291135	COPh	C ₂₆ H ₂₉ NO ₃
291136	COCH2Ph	C ₂₇ H ₃₁ NO ₃
291137	2-Pyr-CO	C ₂₅ H ₂₈ N ₂ O ₃
291138	Me	C ₂₀ H ₂₇ NO ₂
291139	CH2Ph	C ₂₆ H ₃₁ NO ₂

SOURCE – Yamanouchi.

REFERENCES

1. Taniguchi, M. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel quinolone derivs*. JP 2000143632.

ACTION – Adenosine A_{2A} receptor agonist found to be more potent (72-fold) and more selective than the prototype compound CGS-21680 in binding studies using human receptors. Compound prevented tissue inflammation injury caused by lung transplantation, vascular trauma and renal ischemia–reperfusion in preclinical models in rodents. In addition, it could inhibit inflammation in three models of infection: meningitis, infectious arthritis and sepsis. Studies on the mechanism of action of the compound demonstrated that it inhibits neutrophil adhesion and it may also act by inhibiting TNF-α production by inflammatory cells. Compound may also be useful for vasodilator coronary stress imaging.

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ISIS-24195

291063

18-Mer chimeric phosphorothioate oligonucleotide whose sequence is: GGGCGAGTGAGGAAAGGA, in which the central ten nucleosides are 2'-deoxynucleosides, the four nucleosides flanking the 5'- and 3'-ends are 2'-O-(2-methoxyethyl)-substituted nucleosides and the cytidine in position 4 is 2'-O-(2-methoxyethyl)-5-methylcytidine

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SOURCE – Isis Pharmaceuticals.

REFERENCES

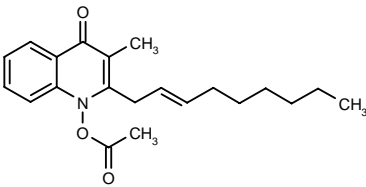
1. Monia, B.P. and Cowsert, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of EGR-1 expression*. WO 0034302.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

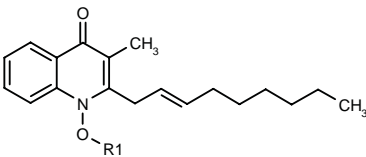
291134

1-Acetoxy-3-methyl-2-[2(E)-nonenyl]quinolin-4(1H)-one



C21 H27 N O3; Mol wt: 341.4483

ACTION – Anti-*Helicobacter pylori* agent from a series of quinolone derivatives wherein the following are also included:



Compound	R1	Formula
291135	COPh	C ₂₆ H ₂₉ NO ₃
291136	COCH2Ph	C ₂₇ H ₃₁ NO ₃
291137	2-Pyr-CO	C ₂₅ H ₂₈ N ₂ O ₃
291138	Me	C ₂₀ H ₂₇ NO ₂
291139	CH2Ph	C ₂₆ H ₃₁ NO ₂

SOURCE – Yamanouchi.

REFERENCES

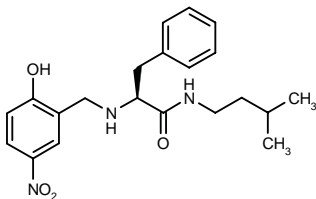
1. Taniguchi, M. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel quinolone derivs*. JP 2000143632.

AGENTS FOR INFLAMMATORY
BOWEL DISEASE

292045

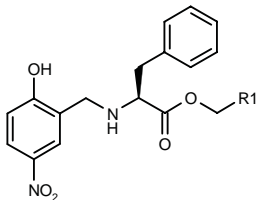
2(S)-(2-Hydroxy-5-nitrobenzylamino)-N-isopentyl-3-phenylpropionamide

N²-(2-Hydroxy-5-nitrobenzyl)-N¹-isopentyl-L-phenylalanylamide



C21 H27 N3 O4; Mol wt: 385.4613

ACTION – An inhibitor of cell adhesion mediated by the leukocyte cell-surface integrin $\alpha_4\beta_7$ and the cell adhesion molecule MAdCAM (IC₅₀ = 6 μ M in B-cell lymphoma RPMI 8866 cells). Potentially useful for the treatment of tissue inflammatory damage in inflammatory bowel disease. Other related phenylalanine-based inhibitors include the following:



Compound	R1	Formula
292046	i-Bu	C ₂₁ H ₂₆ N ₂ O ₅
292047	Ph	C ₂₃ H ₂₂ N ₂ O ₅
292048	t-Bu	C ₂₁ H ₂₆ N ₂ O ₅

SOURCE – Millennium.

REFERENCES

1. Harriman, G.C.B. et al. *Cell adhesion antagonists: Synthesis and evaluation of a novel series of phenylalanine based inhibitors*. Bioorg Med Chem Lett 2000, 10(14): 1497.

TREATMENT OF LIVER AND BILIARY
TRACT DISORDERS

290691

L-Threonyl-L-seryl-L-leucyl-L-aspartyl-L-alanyl-L-seryl-L-isoleucyl-L-isoleucyl-L-tryptophyl-L-alanyl-L-methionyl-L-methionyl-L-glutaminy-L-asparagine

C68 H109 N17 O22 S2; Mol wt: 1580.8380

ACTION – Synthetic peptide derived from human TGF β_1 receptor type III, useful as a TGF β_1 inhibitor for the treatment of hepatic diseases, particularly fibrosis. *In vitro*, compound gave 80% inhibition of the binding of TGF β_1 to its receptors in MV-1-Lu cells at a concentration of 420 μ g/ml and 88% attenuation of TGF β_1 -induced inhibition of MV-1-Lu cell growth at a concentration of 200 μ g/ml. In addition, it was found to be effective in a rat model of experimental cirrhosis induced by CCl₄ following i.p. administration.

SOURCE – Instituto Científico y Tecnológico de Navarra, Pamplona, Navarra (ES).

REFERENCES

1. Ezquerro Saenz, I.J. et al. (Instituto Científico y Tecnológico de Navarra SA) *TGF β_1 inhibitor peptides*. WO 0031135.

ISIS-22023

292486

20-Mer phosphorothioate oligonucleotide whose sequence is: TCCAGCACTTTCTTTTCCGG containing 2'-O-(2-methoxyethyl) modifications at positions 1-5 and 15-20

ACTION – Hepatoprotective agent, an antisense oligonucleotide proven to reduce liver Fas expression both *in vitro* in mouse hepatocyte AML-12 cells and *in vivo* in mouse liver (ID₅₀ = 10 mg/kg/day i.p. x 4). In addition, compound was shown to completely protect mice from fulminant hepatitis induced by administration of the Fas-specific agonist monoclonal antibody Jo-2 when given at a dose of 40 mg/kg i.p. for 4 days and to reduce the severity of acetaminophen-induced fulminant hepatitis at a dose of 24 mg/kg i.p., but it was inactive against concanavalin A-induced hepatitis.

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Zhang, H. et al. *Reduction of liver Fas expression by an antisense oligonucleotide protects mice from fulminant hepatitis*. Nat Biotechnol 2000, 18(8): 862.

PEGINTERFERON alfa-2b

214807

Covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol, with an average molecular weight of approximately 31,300 daltons

Sch-54031

ACTION – Immunostimulant, a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol.

INDICATION – Treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, as monotherapy in cases of intolerance or contraindication to ribavirin.

PRESENTATION – Powder, 50, 80, 100, 120 and 150 µg, with solvent for solution for injection (each vial provides 50, 80, 100, 120 and 150 µg/0.5 ml after reconstitution).

PROPRIETARY NAME – PEG-Intron (DE, GB).

SOURCES – Enzon; marketed by Schering-Plough.

REFERENCES

1. Cutler, D.L. and Affrime, M.B. (Schering Corp.) *Continuous low-dose cytokine infusion therapy*. WO 9716204.

2. Gilbert, C.W. and Cho, M.-O. (Enzon, Inc.) *Improved interferon polymer conjugates*. EP 0730470, JP 1997506087, US 5711944, WO 9513090.

3. Glue, P. et al. (Schering Corp.) *Polyethylene glycol-interferon alpha conjugates for therapy of infection*. WO 9848840.

4. Kline, D.F. (Schering Corp.) *Formulations for protection of PEG-interferon alpha conjugates*. WO 9948535.

5. Laughlin, M.A. et al. (Schering Corp.) *HIV therapy*. WO 0051631.

6. Lee, S. and McNemar, C. (Enzon, Inc.) *Substantially pure histidine-linked protein polymer conjugates*. WO 9932134.

7. Bukowski, R. et al. *Phase I study of polyethylene glycol (PEG) interferon alpha-2B (PEG INTRON) in patients with solid tumors*. Proc Am Soc Clin Oncol 1999, 18: Abst 1719.

8. Feagan, B.G. et al. *The impact of pegylated interferon alfa-2b on health-related quality of life in chronic hepatitis C patients*. Hepatology 2000, 32(4, Part 2): Abst 590.

9. Glue, P. et al. *A dose-ranging study of PEG-intron and ribavirin in chronic hepatitis C - Safety, efficacy, and virologic rationale*. Hepatology 1999, 30(4, Part 2): Abst 571.

10. Glue, P. et al. *A dose-ranging study of pegylated interferon alfa-2b and ribavirin in chronic hepatitis C*. Hepatology 2000, 32(3): 647.

11. Glue, P. et al. *PEG-interferon-alpha2b: Pharmacokinetics, pharmacodynamics, safety and preliminary efficacy data*. Hepatology 1999, 30(4, Part 2): Abst 116.

12. Lindsay, K.L. et al. *Response to PEG-INF alfa-2b (PEG-Intron) in blacks and hispanics with HCV is higher than with standard INF alfa2b (INF)*. Hepatology 2000, 32(4, Part 2): Abst 752.

13. Reynes, J. et al. *Antiretroviral activity and tolerability of PEG-interferon α2b in patients on stable background therapy: Results of a phase I/II study*. 7th Conf Retroviruses Opportunistic Infect (Jan 30-Feb 2, San Francisco) 2000, Abst 542.

14. Takacs, M.A. et al. *Detection and characterization of antibodies to PEG-IFN-α2b using surface plasmon resonance*. J Interferon Cytokine Res 1999, 19(7): 781.

15. Talpaz, M. et al. *Phase I study polyethylene glycol (PEG) interferon α2B (Intron-A) in CML patients*. Blood 1998, 92(10, Suppl. 1, Part 1): Abst 1026.

16. Trepo, C. et al. *Pegylated interferon alf-2b (PEG-Intron) monotherapy is superior to interferon α2b (Intron A) for the treatment of chronic hepatitis C*. 35th Annu Meet Eur Assoc Study Liver (April 29-May 3, Rotterdam) 2000, Abst GS2/07.

17. *BLA submitted for PEG-Intron HCV therapy*. DailyDrugNews.com (Daily Essentials) 2000, Jan 10.

18. *CPMP issues positive opinion regarding PEG-Intron MAA*. DailyDrugNews.com (Daily Essentials) 2000, Feb 23.

19. *Enzon and Schering-Plough revise agreement for PEG-Intron*. DailyDrugNews.com (Daily Essentials) 1999, June 30.

20. *Enzon completes know-how transfer to Schering Corporation for PEG-INTRON A*. Enzo, Inc. Press Release 1996, Oct 9.

21. *Enzon initiates phase III trials of PEG-Intron/Rebetol combination therapy for hepatitis C*. DailyDrugNews.com (Daily Essentials) 1999, Feb 3.

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27. *PEG-Intron A progresses to phase III for treatment of hepatitis C*. DailyDrugNews.com (Daily Essentials) 1997, Aug 5.

28. *PEG-Intron at least as effective and safe as Intron A in phase III HCV trial*. DailyDrugNews.com (Daily Essentials) 2000, April 28.

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30. *PEG-Intron submitted for marketing approval in Europe*. DailyDrugNews.com (Daily Essentials) 1999, Nov 22.

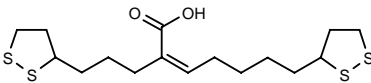
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ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

290674

7-(1,2-Dithiolan-3-yl)-2-[3-(1,2-dithiolan-3-yl)propyl]-2(Z)-heptenoic acid



C16 H26 O2 S4; Mol wt: 378.6434

PEGINTERFERON alfa-2b

214807

Covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol, with an average molecular weight of approximately 31,300 daltons

Sch-54031

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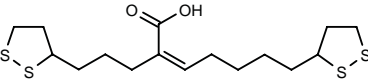
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ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

290674

7-(1,2-Dithiolan-3-yl)-2-[3-(1,2-dithiolan-3-yl)propyl]-2(Z)-heptenoic acid



C16 H26 O2 S4; Mol wt: 378.6434

ACTION – Lipoic acid analogue with free radical-, metal- and reactive oxygen species (ROS)-scavenging activity, potentially useful for the treatment of conditions associated with oxidative stress or free radical injury such as aging, pulmonary and ocular hypertension, asthma, trauma, neurological and neurodegenerative diseases, gastrointestinal disorders, inflammatory bowel disease, neuropathies and nephropathies, aggregation disorders and male impotence, as well as for retarding the development of tolerance to classical nitric oxide (NO) donors. Compound was found to prevent tolerance development to nitroglycerin in rats at a dose of 50 mg/kg i.p. In addition, it exhibited protective activity against streptozotocin-induced diabetes in rats and was effective in the acetic acid-induced colitis model in rats.

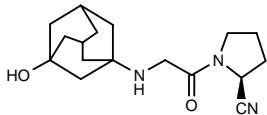
SOURCE – Yissum.

REFERENCES

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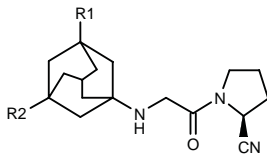
291074

1-[2-(3-Hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(S)-carbonitrile

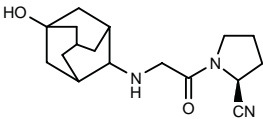


C17 H25 N3 O2; Mol wt: 303.4035

ACTION – Dipeptidyl-peptidase IV (DPP-IV) inhibitor (IC_{50} = 3.5 ± 1.5 nM in human colon carcinoma Caco-2 cells expressing DPP-IV; IC_{50} = 2.7 ± 0.1 and 2.3 ± 0.1 nM in human and rat plasma, respectively). The compound was also found to increase the early insulin response to an oral glucose challenge by 64% at an oral dose of 10 μ mol/kg in rats. It is expected to be of use in the treatment of non-insulin-dependent diabetes mellitus. Other specifically claimed *N*-substituted 2-cyanopyrrolidines are:



Compound	R1	R2	Formula
291075	Me	Me	C ₁₉ H ₂₉ N ₃ O
291076	H	Et	C ₁₉ H ₂₉ N ₃ O
291077	H	OMe	C ₁₉ H ₂₇ N ₃ O ₂
291078	H	t-BuNHCOO	C ₂₂ H ₃₄ N ₄ O ₃
291079	H	4-MeO-PhNHCOO	C ₂₅ H ₃₂ N ₄ O ₄
291080	H	OCNHPh	C ₂₄ H ₃₀ N ₄ O ₃
291082	H	OAc	C ₁₉ H ₂₇ N ₃ O ₃
291083	H	OCON(i-Pr) ₂	C ₂₄ H ₃₈ N ₄ O ₃
291084	H	cyclohexyl-NHCOO	C ₂₄ H ₃₆ N ₄ O ₃
291085	H	OEt	C ₁₉ H ₂₉ N ₃ O ₂



291081: C17 H25 N3 O2

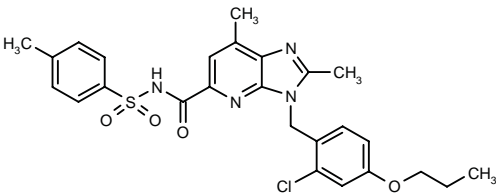
SOURCE – Novartis.

REFERENCES

1. Villhauer, E.B. (Novartis AG) *N-Substd. 2-cyanopyrrolidines.* WO 0034241.

291125

3-(2-Chloro-4-propoxybenzyl)-2,7-dimethyl-*N*-(4-methylphenylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxamide



C26 H27 Cl N4 O4 S; Mol wt: 527.0423

ACTION – Hypoglycemic agent proven to reduce blood glucose levels by 97% in *db/db* mice at a dose of 1 mg/kg in the diet. A representative compound from a series of sulfonamide derivatives also reported to inhibit cGMP phosphodiesterase and to exert smooth muscle relaxant, bronchodilating and antiallergic effects.

SOURCE – Fujisawa.

REFERENCES

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291282

H-His-Aib-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Aib-Gly-NH₂

[Aib^{8,35}]-hGLP-1(7-37)NH₂

C152 H232 N40 O45; Mol wt: 3339.7400

ACTION – Glucagon-like peptide-1 (GLP-1) analogue with an agonist effect on GLP-1 receptors. Claimed particularly for the treatment of type 1 and type 2 diabetes, as well as obesity, airways secretory disorders, metabolic disorders, arthritis, osteoporosis, CNS disorders, neurodegenerative diseases, renal and congestive heart failure, cirrhosis, pulmonary edema and hypertension.

SOURCE – SCRAS.

REFERENCES

1. Dong, Z.X. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Analogues of GLP-1.* WO 0034331.

291288

H-His-D-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ala-Ser-3-Pal-Leu-Glu-Ala-Ala-Ala-Lys-Ala-Phe-Ile-Ala-3-Pal-Leu-Val-Lys-Gly-Arg- γ -aminobutyric acid

C132 H201 N35 O38; Mol wt: 2886.2470

ACTION – Glucagon-like peptide-1 (GLP-1) analogue with an agonist effect on GLP-1 receptors. Claimed particularly for the treatment of type 1 and type 2 diabetes, as well as obesity, airways secretory disorders, metabolic disorders, arthritis, osteoporosis, CNS disorders, neurodegenerative diseases, renal and congestive heart failure, cirrhosis, pulmonary edema and hypertension.

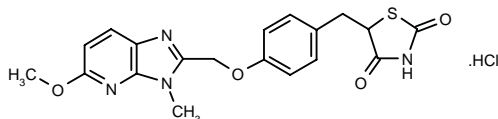
SOURCES – SCRAS; Tulane Educational Fund, New Orleans, LA (US).

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291707

5-[4-(5-Methoxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione hydrochloride



C19 H18 N4 O4 S . HCl; Mol wt: 434.9021

ACTION – Hypoglycemic agent, an imidazopyridine thiazolidinedione obtained by chemical modification of rosiglitazone, proven to lower blood glucose levels in KK mice with an ED₂₅ of 0.02 mg/kg/day p.o. for 1 week versus 0.39 mg/kg/day for the maleate salt of rosiglitazone. *In vitro*, compound stimulated adipogenesis in 3T3-L1 cells with an EC₅₀ of 0.11 μ M. It is reported to be associated with less cardiac hypertrophy compared to rosiglitazone and has been selected as a candidate for development in the treatment of type 2 diabetes.

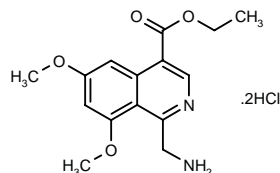
SOURCE – Sankyo.

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292049

1-(Aminomethyl)-6,8-dimethoxyisoquinoline-4-carboxylic acid ethyl ester dihydrochloride



C15 H18 N2 O4 . 2HCl; Mol wt: 363.2390

ACTION – Dipeptidyl-peptidase IV inhibitor (IC₅₀ = 0.32 μ M) proven to be about 53-fold more potent than the parent compound SDZ-029576 (IC₅₀ = 17 μ M). Potentially useful for the treatment of type 2 diabetes.

SOURCE – Novartis.

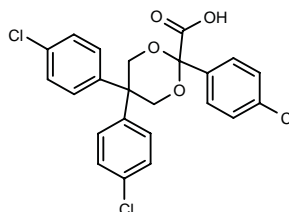
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2. Coppola, G.M. et al. *Isoquinoline-based amino acid derivatives*. Heterocycl Commun 2000, 6(1): 13.

LR-90

292538

2,5,5-Tris(4-chlorophenyl)-1,3-dioxane-2-carboxylic acid



C23 H17 Cl3 O4; Mol wt: 463.7423

ACTION – Hypoglycemic and hypolipidemic agent shown to activate both peroxisome proliferator-activated receptors PPAR α and PPAR β in a transactivation assay. In *db/db* mice, compound given at a dose of 100 mg/kg/day p.o. for 15 day decreased plasma glucose and triglycerides by 44 and 59%, respectively. Potentially useful for the treatment of diabetes, dyslipidemia and atherosclerosis.

SOURCE – Lipha.

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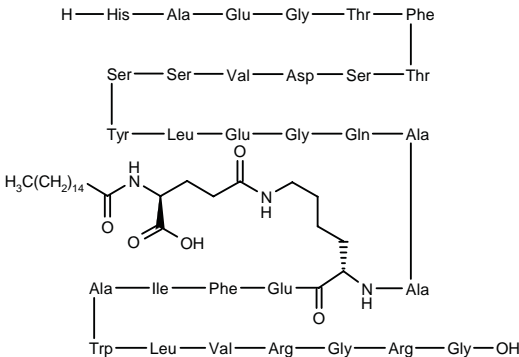
1. Berthelon, J.-J. et al. (Merck Patent GmbH) *Cyclic cpds. useful in the treatment of dyslipidaemia, atherosclerosis and diabetes, pharmaceutical compsns. and preparation process*. FR 2781222, WO 0004011.
2. Zeiller, J.-J. et al. *LR 90, a new compound with both hypolipidemic and hypoglycemic activities*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MED1 308.

NN-2211*

288055

L-Histidyl-L-alanyl-L-glutamyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-glutamyl-glycyl-L-glutaminyl-L-alanyl-L-alanyl-*N*^ε-(*N*^α-hexadecanoyl-γ-L-glutamyl)-L-lysyl-L-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginyl-glycyl-L-arginyl-glycine

NNC-90-1170



C172 H265 N43 O51; Mol wt: 3751.2360

ACTION – Potent and metabolically stable glucagon-like peptide-1 (GLP-1) analogue with an EC₅₀ of 61 pM in a functional assay in BHK cells expressing cloned human GLP-1 receptors. In *ob/ob* mice, compound significantly reduced blood glucose levels, food intake and body weight in a dose-dependent manner (30, 100, 300 and 1000 µg/kg s.c.) after a single dose, with peak effect on blood glucose at 10 h. In ZDF diabetic rats, 6-week treatment with compound at 30 and 150 µg/kg induced a marked attenuation of the progression of diabetes, as demonstrated by reductions in blood glucose and food intake and increase in insulin. An increase in pancreatic β-cell mass was also seen in animals treated with compound. Compound is undergoing phase I clinical studies as a potential treatment for type 2 diabetes.

SOURCES – Novo Nordisk; Scios.

REFERENCES

1. Knudsen, L.B. et al. (Novo Nordisk A/S) *GLP-1 derivs. with helix-content exceeding 25%, forming partially structured micellar-like aggregates*. WO 9943341, WO 9943706.
2. Knudsen, L.B. et al. *Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration*. J Med Chem 2000, 43(9): 1664.
3. Larsen, M.O. et al. *NN2211, a long-acting derivative of GLP-1, lowers blood glucose in ob/ob and db/db mice*. Diabetes 2000, 49(Suppl. 1): Abst 4-OR.
4. Larsen, P.J. et al. *Systemic administration of the long-acting GLP-1 derivative, NN2211, induces lasting and reversible loss of body adiposity*. Diabetes 2000, 49(Suppl. 1): Abst 243-OR.
5. Rolin, B. et al. *Efficacy of the long-acting GLP-1 derivative NN 2211 in diabetic ob/ob mice*. Diabetes 2000, 49(Suppl. 1): Abst 942-P.
6. Sturis, J. et al. *The long-acting GLP-1 derivative NN2211 markedly slows the development of diabetes in the male Zucker diabetic fatty rat*. Diabetes 2000, 49(Suppl. 1): Abst 943-P.

*Identified compound **288055** Drug Data Rep 2000, 022(07): 0615.

TREATMENT OF GYNECOLOGICAL DISORDERS

XENOXIN-1

290896

H-Leu-Lys-Cys-Val-Asn-Leu-Gln-Ala-Asn-Gly-Ile-Lys-Met-Thr-Gln-Glu-Cys-Ala-Lys-Glu-Asp-Thr-Lys-Cys-Leu-Thr-Leu-Arg-Ser-Leu-Lys-Lys-Thr-Leu-Lys-Phe-Cys-Ala-Ala-Ser-Gly-Arg-Thr-Cys-Thr-Thr-Met-Lys-Ile-Met-Ser-Leu-Pro-Gly-Glu-Gln-Ile-Thr-Cys-Cys-Glu-Gly-Asn-Met-Cys-Asn-Ala-OH

C299 H517 N87 O95 S12; Mol wt: 7235.6790

ACTION – Member of a new family of peptides isolated from skin secretions of the frog *Xenopus laevis* that act as modulators of transmembrane ion channels and activin, while being devoid of neurotoxicity. These peptides are expected to be of use for the treatment of cardiac arrhythmias, cystic fibrosis and disorders related to an imbalance of human chorionic gonadotropin during pregnancy or the secretion of the hormones FSH, STH and ACTH. Other peptides form this family are:

H-Leu-Lys-Cys-Val-Asn-Leu-Gln-Ala-Asn-Gly-Ile-Lys-Met-Thr-Gln-Glu-Cys-Ala-Lys-Glu-Asp-Asn-Lys-Cys-Leu-Thr-Leu-Arg-Ser-Leu-Lys-Lys-Thr-Leu-Lys-Phe-Cys-Ala-Ser-Asp-Arg-Ile-Cys-Lys-Thr-Met-Lys-Ile-Met-Ser-Leu-Pro-Gly-Glu-Lys-Ile-Thr-Cys-Cys-Glu-Gly-Asn-Met-Cys-Asn-Ala-OH

Xenoxin-2 [290898]: C306 H531 N89 O94 S12

H-Leu-Lys-Cys-Val-Asn-Leu-Gln-Ala-Asn-Gly-Val-Lys-Met-Thr-Gln-Glu-Cys-Ala-Lys-Glu-Asp-Thr-Lys-Cys-Leu-Thr-Leu-Arg-Ser-Leu-Lys-Lys-Thr-Leu-Lys-Phe-Cys-Ala-Ser-Asp-Arg-Ile-Cys-Lys-Thr-Met-Lys-Ile-Ala-Ser-Leu-Pro-Gly-Glu-Gln-Ile-Thr-Cys-Cys-Glu-Gly-Asn-Met-Cys-Asn-Ala-OH

Xenoxin-3 [290899]: C302 H522 N88 O95 S11

SOURCE – Transgene.

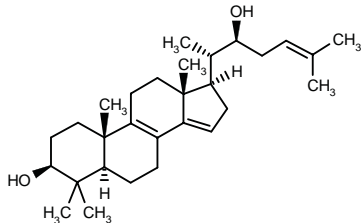
REFERENCES

1. Kolbe, H.V.J. et al. (Transgene SA) *Family of peptides known as xenoxins*. US 6077827, WO 9501431.

AGENTS FOR FEMALE INFERTILITY

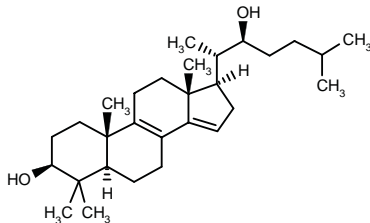
291624

(3β,5α,20S,22S)-4,4-Dimethylcholesta-8,14,24-triene-3,22-diol



C29 H46 O2; Mol wt: 426.6804

ACTION – Potent meiosis activator potentially useful as a fertility control agent. Compound was able to overcome hypoxanthine-maintained meiotic arrest in denuded oocytes (DO) and in cumulus-enclosed oocytes (CEO), with a percentage of germinal vesicle breakdown of 97 and 73% in DO and CEO, respectively, following culturing in the presence of compound at 5 μM. An exemplified compound from a series of 22S-hydroxycholesta-8,14-diene derivatives, wherein the following is also included:



291625: C29 H48 O2

SOURCE – Akzo Nobel.

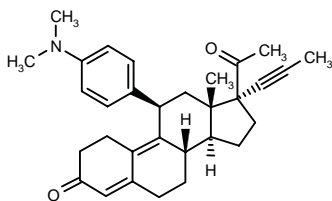
REFERENCES

1. Leysen, D. et al. (Akzo Nobel N.V.) 22S-Hydroxycholesta-8,14-diene derivs. with meiosis regulating activity. WO 0035938.

CONTRACEPTIVES

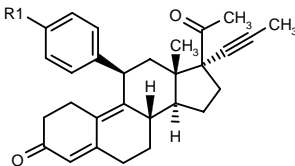
291303

17β-Acetyl-11β-[4-(dimethylamino)phenyl]-17α-(1-propynyl)estra-4,9-dien-3-one



C31 H37 N O2; Mol wt: 455.6383

ACTION – Potent progestin antagonist proven to bind to the progestin receptor in human breast carcinoma T-47D cells with a relative binding activity (RBA) of 313% that of promegestone. *In vivo*, compound exhibited significantly more potent antiprogestational activity than mifepristone in estrogen-primed, progesterone-stimulated immature female rabbits following oral administration. Potentially useful for the treatment of fibroids, endometriosis and certain tumors, as well as for inducing cervical ripening prior to delivery, in hormone replacement therapy and for the control of fertility and reproduction. Other exemplified compounds from this series of 17β-acyl-17α-propynyl-11β-arylsteroids include the following:



Compound	R1	Formula
291304	Ac	C ₃₁ H ₃₄ O ₃
291305	SMe	C ₃₀ H ₃₄ O ₂ S

SOURCE – Research Triangle Institute, Research Triangle Park, NC (US).

REFERENCES

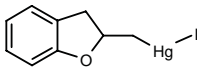
1. Cook, C.E. et al. (Research Triangle Institute) 17β-Acyl-17α-propynyl-11β-arylsteroids and their derivs. having agonist or antagonist hormonal properties. WO 0034306.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

290687

(2,3-Dihydrobenzofuran-2-ylmethyl)(iodo)mercury(II)



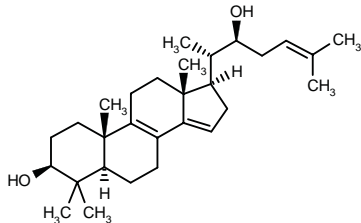
C9 H9 Hg I O; Mol wt: 460.6591

ACTION – Agent for the treatment of proliferative disorders, blood or bone marrow disorders and microbial infections, a representative compound from a series of 5'-substituted 4',5'-dihydropsoralen derivatives reported to exhibit reduced mutagenic/carcinogenic potential compared to previous psoralens by virtue of their inability to form crosslinks in DNA. Due to the presence of a mercury functionality, compound exhibits a unique cytotoxicity profile, being cytotoxic without light activation and showing enhanced cytotoxicity upon light activation, as demonstrated *in vitro* in keratinocyte PAM212 cultures by IC₅₀ values of 5.7 and 12 μM, respectively, with and without exposure to UVA light. In addition, it exhibited antifungal activity against *Aspergillus niger* and algicidal activity, and it produced 99% inhibition of *Mycobacterium tuberculosis* H37Rv at 12.5 μg/ml.

AGENTS FOR FEMALE INFERTILITY

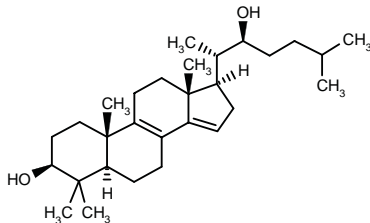
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C29 H46 O2; Mol wt: 426.6804

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SOURCE – Akzo Nobel.

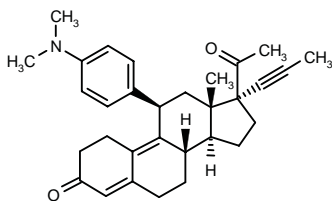
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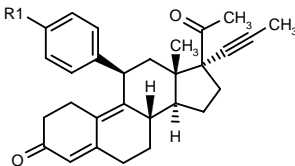
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SOURCE – Research Triangle Institute, Research Triangle Park, NC (US).

REFERENCES

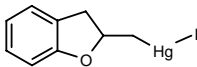
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DERMATOLOGIC DRUGS

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290687

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ACTION – Agent for the treatment of proliferative disorders, blood or bone marrow disorders and microbial infections, a representative compound from a series of 5'-substituted 4',5'-dihydropsoralen derivatives reported to exhibit reduced mutagenic/carcinogenic potential compared to previous psoralens by virtue of their inability to form crosslinks in DNA. Due to the presence of a mercury functionality, compound exhibits a unique cytotoxicity profile, being cytotoxic without light activation and showing enhanced cytotoxicity upon light activation, as demonstrated *in vitro* in keratinocyte PAM212 cultures by IC₅₀ values of 5.7 and 12 μM, respectively, with and without exposure to UVA light. In addition, it exhibited antifungal activity against *Aspergillus niger* and algicidal activity, and it produced 99% inhibition of *Mycobacterium tuberculosis* H37Rv at 12.5 μg/ml.

SOURCE – Buckman Laboratories.

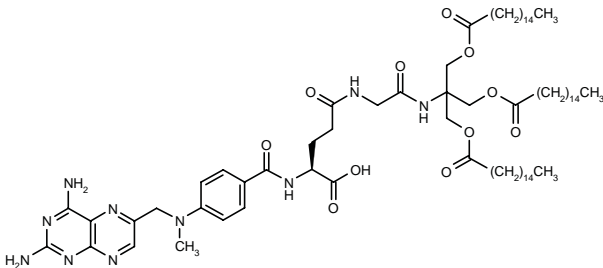
REFERENCES

1. Heindel, N.D. et al. (Buckman Laboratories International, Inc.) *Amino- and mercurio-substd. 4',5'-dihydropsoalens and therapeutical uses thereof*. WO 0031081.

291141

N^α-[4-[*N*-(2,4-Diamino-6-pteridinylmethyl)-*N*-methyl-amino]benzoyl]-*N*^δ-[2-[2-(hexadecanoyloxy)-1,1-bis(hexadecanoyloxymethyl)ethylamino]-2-oxoethyl]-L-glutamine

MTX-γ-GTP-3



C74 H124 N10 O11; Mol wt: 1329.8530

ACTION – Antipsoriatic agent, a methotrexate conjugate with reduced toxicity and comparable or increased activity as compared to the parent drug. Compound exhibited equivalent or better activity compared to methotrexate in reducing UVB-induced epidermal hyperproliferation in hairless mice and suppressed UVB-induced epidermal DNA synthesis following topical application. In addition, distribution studies in hairless mice using this compound showed that it has increased skin retention compared to methotrexate following topical application, and it was further shown to be less toxic in these animals than methotrexate following topical or oral administration. Compound was further tested topically in a clinical trial assessing antipsoriatic activity based on the small plaque assay (SPA), where it exhibited positive effects on filaggrin expression, granularity and parakeratosis in 5 of 11 patients.

SOURCE – CSIRO, Clayton (AU).

REFERENCES

1. Whittaker, R.G. et al. (CSIRO [Commonwealth Scientific and Industrial Research Organisation]) *Methotrexate derivs*. WO 0034281.

ISIS-12854

291070

20-Mer mixed-backbone chimeric oligonucleotide whose sequence is: 5'-TCCGCCTGTGACATGCATT-3', in which the central eight nucleosides are 2'-deoxynucleosides, the last six nucleosides flanking the 5'- and 3'-ends are 2'-O-(2-methoxyethyl)-substituted nucleosides, the linkages between nucleosides in positions 1-2, 2-3, 3-4, 4-5, 5-6, 15-16, 16-17, 17-18, 18-19, 19-20 are phosphodiester linkages while the others are phosphorothioate linkages, and cytidines in positions 2, 3, 4, 6 and 17 are 2'-O-(2-methoxyethyl)-5-methylcytidines

ACTION – Chimeric antisense oligonucleotide targeted to mRNA encoding *c-raf*, potentially useful for modulating the expression of cell adhesion molecules through inhibition of *c-raf* signaling pathways, and consequently, for the treatment of diseases associated with overexpression of cell adhesion molecules, particularly inflammatory and immune diseases. Compound inhibited *c-raf* mRNA levels in human dermal microvascular cells (HMVEC) with an IC₅₀ value of < 2.5 nM. In addition, it inhibited cell surface expression of E-selectin, ICAM-1 and VCAM-1 by 74, 43 and 72% at 75, 100 and 100 nM, respectively, in HMVEC cells, and this effect was shown to occur at the transcriptional level (78, 22 and 65% inhibition of E-selectin, ICAM-1 and VCAM-1 mRNA levels, respectively). Compound was further shown to inhibit *in vitro* TNF-stimulated ERK and JKN activity. Another exemplified oligonucleotide from this series of inhibitors of signaling molecules involved in human TNF-α signaling is:

20-Mer mixed-backbone chimeric oligonucleotide whose sequence is: 5'-TCCGTCATCGCTCCTCAGGG-3', in which the first three nucleosides flanking the 5'-end and the last eight nucleosides flanking the 3'-end are 2'-O-(2-methoxyethyl)-substituted nucleosides, the central nine nucleosides are 2'-deoxynucleosides, the linkages between nucleosides in positions 1-2, 2-3, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20 are phosphodiester linkages while the others are phosphorothioate linkages, and cytidines in positions 2, 3, 13, 14, and 16 are 2'-O-(2-methoxyethyl)-5-methylcytidines

ISIS-15168 [291072]

SOURCE – Isis Pharmaceuticals.

REFERENCES

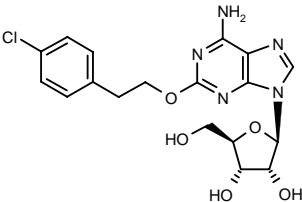
1. Monia, B.P. and Xu, X.S. (Isis Pharmaceuticals, Inc.) *Methods of modulating tumor necrosis factor α-induced expression of cell adhesion molecules*. US 6114517, WO 0034303.

WOUND-HEALING AGENTS

MRE-0094

291379

2-[2-(4-Chlorophenyl)ethoxy]adenosine



C18 H20 Cl N5 O5; Mol wt: 421.8390

ACTION – Potent and selective adenosine A₂ receptor agonist with pEC₅₀ values of 9.41 and 4.84 for agonist potency in guinea pig coronary arteries and atrioventricular node (A₂ and A₁ receptors, respectively). The local application of compound (1 and 10 μg/wound) to wounds on the back of mice was shown to produce 50% wound closure significantly faster than the control, indicating that the adenosine A₂ agonist promotes wound closure. Potentially useful for the treatment of poorly healing wounds.

SOURCE – Medco.

REFERENCES

1. Daly, J.W. et al. *Structure-activity relationships for 2-substituted adenosines at A₁ and A₂ adenosine receptors*. Pharmacology 1993, 46(2): 91.

2. Famini, G.R. et al. *Using theoretical descriptors in a correlation analysis of adenosine activity*. Quant Struct-Act Relatsh 1998, 17(6): 558.

3. Matova, M. et al. *QSAR analysis of 2-alkyloxy and 2-aralkyloxy adenosine A₁- and A₂-agonists*. Eur J Med Chem 1997, 32(6): 505.

4. Matova, M.M. et al. *Molecular modeling of 2-alkyloxy- and 2- aralkyloxy-adenosine A₁- and A₂-agonists*. Drug Des Discov 2000, 16(4): 255.

5. Ueeda, M. et al. *2-Aralkoxyadenosines: Potent and selective agonists at the coronary artery A₂ adenosine receptor*. J Med Chem 1991, 34(4): 1340.

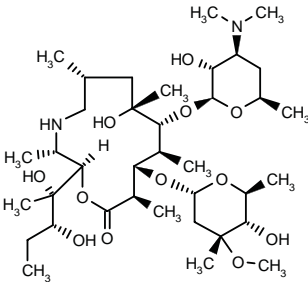
6. Victor-Vega, C. et al. *Adenosine A_{2A} receptor agonists promote more rapid wound healing than recombinant platelet derived growth factor (PDGF)*. Drug Dev Res 2000, 50(1): Abst 146.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

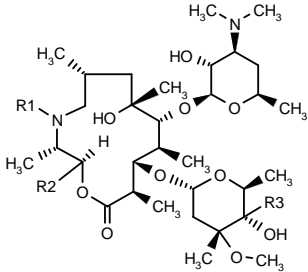
290709

13-Desethyl-11,12-dideshydroxy-10-desmethyl-13-[1(S),2(S)-dihydroxy-1-methylbutyl]-11-aza-9-nor-erythromycin A



C37 H70 N2 O12; Mol wt: 734.9620

ACTION – Antibacterial and antiprotozoal agent, a representative compound from a series of 13-membered azalides, wherein the following are also included:



Compound	R1	R2	R3	Formula
290710	H	(E)-COCH=CHN(Me)2	H	C ₃₇ H ₆₇ N ₃ O ₁₁
290711	Me	Ac	H	C ₃₅ H ₆₄ N ₂ O ₁₁
290712	Me	1-(3-OH-PhCH2)-3-pyrazolyl	H	C ₄₃ H ₇₀ N ₄ O ₁₁
290713	Me	1-Me-3-pyrazolyl	H	C ₃₇ H ₆₆ N ₄ O ₁₀

Compound	R1	R2	R3	Formula
290714	H	(S,S)-C(Me)(OH)CH(OH)Et	CH2NHPr	C ₄₁ H ₇₉ N ₃ O ₁₂
290715	H	5(R)-Et-4(S)-Me-2-oxo-dioxolan-4-yl	CH2NHPr	C ₄₂ H ₇₇ N ₃ O ₁₃

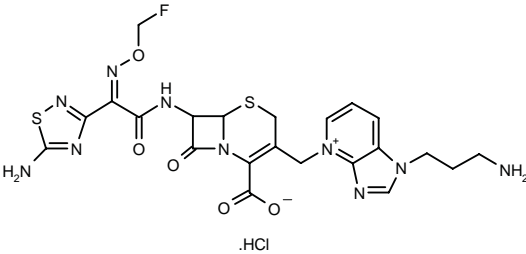
SOURCE – Pfizer.

REFERENCES

1. Rafka, R.J. et al. (Pfizer Products Inc.) *13-Membered azalides and their use as antibiotic agents*. WO 0031097.

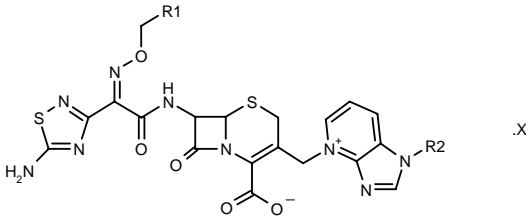
290909

3-[1-(3-Aminopropyl)-1*H*-imidazo[4,5-*b*]pyridin-4-iumyl-methyl]-7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(fluoromethoxyimino)acetamido]-3-cephem-4-carboxylate hydrochloride



C22 H23 F N10 O5 S2 . HCl; Mol wt: 627.0796

ACTION – Cephem antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative microorganisms including methicillin-resistant *Staphylococcus aureus* (MRSA), e.g., *S. aureus* Smith and *S. aureus* SR14 (MIC = 0.78 µg/ml), *S. aureus* SR3626 and SR3637 (MIC = 3.13 µg/ml), *Streptococcus pneumoniae* type 1 (MIC = 0.025 µg/ml), *Escherichia coli* NIH JC-2 (MIC = 0.1 µg/ml), etc. It was also active against *S. aureus* SR3637 infection in mice. Other exemplified cepems containing an imidazo[4,5-*b*]pyridiniummethyl moiety are:



Compound	R1	R2	X	Formula
290910	Me	3(S)-pyrrolidinyl		C ₂₄ H ₂₆ N ₁₀ O ₅ S ₂
290911	Me	(CH2)3NHMe	HCl	C ₂₄ H ₂₈ N ₁₀ O ₅ S ₂ ·HCl
290912	F	(CH2)3NHMe	HCl	C ₂₃ H ₂₅ FN ₁₀ O ₅ S ₂ ·HCl
290913	Me	(CH2)3NH2	HCl	C ₂₃ H ₂₆ N ₁₀ O ₅ S ₂ ·HCl

SOURCE – Shionogi.

REFERENCES

1. Nishitani, Y. et al. (Shionogi & Co. Ltd.) *Imidazo[4,5-*b*]pyridiniummethyl-containing cephem cpds. having broad antibacterial spectrum*. WO 0032606.

SOURCE – Medco.

REFERENCES

1. Daly, J.W. et al. *Structure-activity relationships for 2-substituted adenosines at A₁ and A₂ adenosine receptors*. Pharmacology 1993, 46(2): 91.

2. Famini, G.R. et al. *Using theoretical descriptors in a correlation analysis of adenosine activity*. Quant Struct-Act Relatsh 1998, 17(6): 558.

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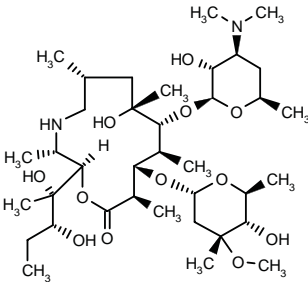
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ANTIINFECTIVE THERAPY

ANTIBIOTICS

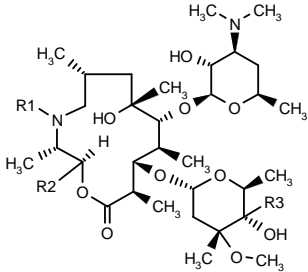
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290712	Me	1-(3-OH-PhCH2)-3-pyrazolyl	H	C ₄₃ H ₇₀ N ₄ O ₁₁
290713	Me	1-Me-3-pyrazolyl	H	C ₃₇ H ₆₆ N ₄ O ₁₀

Compound	R1	R2	R3	Formula
290714	H	(S,S)-C(Me)(OH)CH(OH)Et	CH2NHPr	C ₄₁ H ₇₉ N ₃ O ₁₂
290715	H	5(R)-Et-4(S)-Me-2-oxo-dioxolan-4-yl	CH2NHPr	C ₄₂ H ₇₇ N ₃ O ₁₃

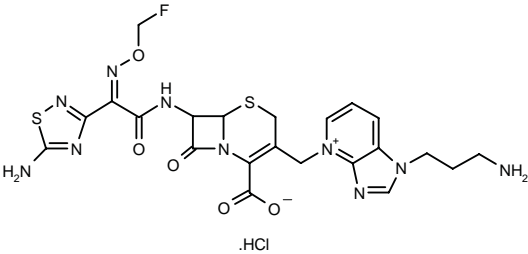
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REFERENCES

1. Rafka, R.J. et al. (Pfizer Products Inc.) *13-Membered azalides and their use as antibiotic agents*. WO 0031097.

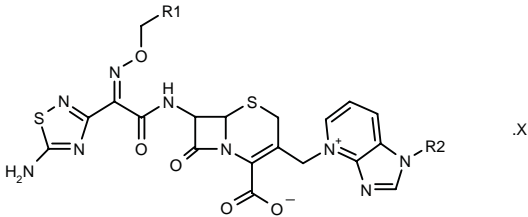
290909

3-[1-(3-Aminopropyl)-1*H*-imidazo[4,5-*b*]pyridin-4-iumyl-methyl]-7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(fluoromethoxyimino)acetamido]-3-cephem-4-carboxylate hydrochloride



C22 H23 F N10 O5 S2 . HCl; Mol wt: 627.0796

ACTION – Cephem antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative microorganisms including methicillin-resistant *Staphylococcus aureus* (MRSA), e.g., *S. aureus* Smith and *S. aureus* SR14 (MIC = 0.78 µg/ml), *S. aureus* SR3626 and SR3637 (MIC = 3.13 µg/ml), *Streptococcus pneumoniae* type 1 (MIC = 0.025 µg/ml), *Escherichia coli* NIH JC-2 (MIC = 0.1 µg/ml), etc. It was also active against *S. aureus* SR3637 infection in mice. Other exemplified cepems containing an imidazo[4,5-*b*]pyridiniummethyl moiety are:



Compound	R1	R2	X	Formula
290910	Me	3(S)-pyrrolidinyl		C ₂₄ H ₂₆ N ₁₀ O ₅ S ₂
290911	Me	(CH2)3NHMe	HCl	C ₂₄ H ₂₈ N ₁₀ O ₅ S ₂ ·HCl
290912	F	(CH2)3NHMe	HCl	C ₂₃ H ₂₅ FN ₁₀ O ₅ S ₂ ·HCl
290913	Me	(CH2)3NH2	HCl	C ₂₃ H ₂₆ N ₁₀ O ₅ S ₂ ·HCl

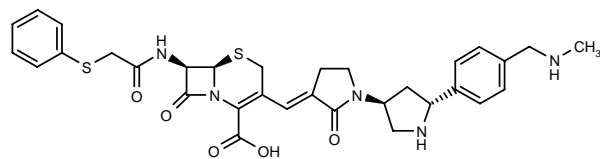
SOURCE – Shionogi.

REFERENCES

1. Nishitani, Y. et al. (Shionogi & Co. Ltd.) *Imidazo[4,5-*b*]pyridiniummethyl-containing cephem cpds. having broad antibacterial spectrum*. WO 0032606.

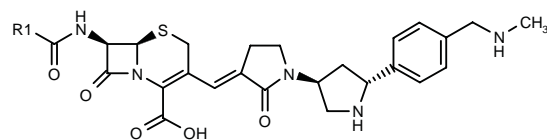
290931

(6*R*,7*R*)-3-[1-[5(*R*)-[4-(Methylaminomethyl)phenyl]pyrrolidin-3(*S*)-yl]-2-oxopyrrolidin-3(*E*)-ylidenemethyl]-7-[2-(phenylsulfanyl)acetamido]-3-cephem-4-carboxylic acid



C32 H35 N5 O5 S2; Mol wt: 633.7905

ACTION – Cephalosporin antibiotic active against Gram-positive bacteria, especially sensitive and resistant staphylococci, pneumococci and enterococci. *In vitro*, compound gave MIC values against *Staphylococcus aureus* 887 (MSSA) and *S. aureus* 270A (MRSA) of 2 and 1 µg/ml, respectively. Other specifically claimed compounds from this series of bi-pyrrolidinylvinyl cephalosporins are:



Compound	R1	Formula
290932	2-Naph-SCH2	C ₃₆ H ₃₇ N ₅ O ₅ S ₂
290933	6-CO2H-2-Naph-SCH2	C ₃₇ H ₃₇ N ₅ O ₇ S ₂
290934	5-NH2-1,2,4-thiadiazol-3-yl-C(=NOH)	C ₂₈ H ₃₁ N ₉ O ₆ S ₂
290935	2-NH2-4-thiazolyl-C(=NOH)	C ₂₉ H ₃₂ N ₈ O ₆ S ₂

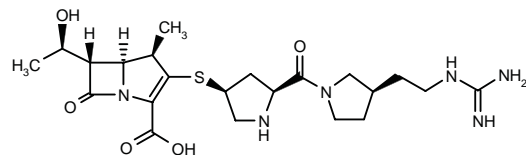
SOURCE – Roche.

REFERENCES

1. Hebeisen, P. et al. (F. Hoffmann-La Roche AG) *Bi-pyrrolidinylvinyl (carba) cephalosporins*. WO 0032605.

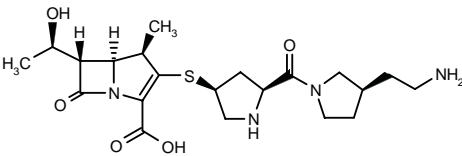
291060

(1*R*,5*S*,6*S*)-3-[5(*S*)-[3(*S*)-(2-Guanidinoethyl)pyrrolidin-1-ylcarbonyl]pyrrolidin-3(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid



C22 H34 N6 O5 S; Mol wt: 494.6136

ACTION – Carbapenem antibiotic with excellent antibacterial activity, active against *Staphylococcus aureus* 209P, *Enterococcus faecalis* 681, *Escherichia coli* NIHJ, *E. coli* 609, *Enterobacter cloacae* 963, *Proteus vulgaris* 1420, *Morganella morganii* 1510, *Pseudomonas aeruginosa* 1001 and *P. aeruginosa* No7 (MIC = 0.012-0.20 µg/ml). Another exemplified 1-methylcarbapenem derivative is:



291062: C21 H32 N4 O5 S

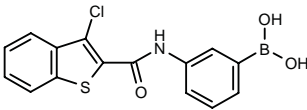
SOURCE – Sankyo.

REFERENCES

1. Kawamoto, I. et al. (Sankyo Co., Ltd.) *1-Methylcarbapenem derivs.* JP 2000229969, WO 0034282.

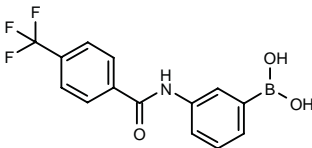
291501

3-(3-Chlorobenzothien-2-ylcarboxamido)phenylboronic acid



C15 H11 B Cl N O3 S; Mol wt: 331.5859

ACTION – An inhibitor of β-lactamases (IC₅₀ = 1.6 µM against AmpC β-lactamase from *Escherichia coli*) with potential for the treatment of β-lactam antibiotic-resistant bacterial infections in combination with β-lactam antibiotics. Another compound from this series of boronic acid derivatives is:



291502: C14 H11 B F3 N O3

SOURCES – Università degli Studi di Modena, Modena (IT); Northwestern University, Evanston, IL (US).

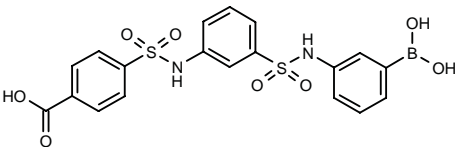
REFERENCES

1. Shoichet, B.K. et al. (Università degli Studi di Modena e Reggio Emilia;Northwestern University) *Inhibitors of β-lactamases and uses therefor*. WO 0035905.

291503

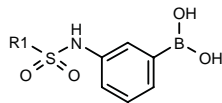
4-[*N*-[3-[*N*-[3-(Dihydroxyboranyl)phenyl]sulfamoyl]-phenyl]sulfamoyl]benzoic acid

3-[3-(4-Caboxyphenylsulfonamido)phenylsulfonamido]-phenylboronic acid



C19 H17 B N2 O8 S2; Mol wt: 476.2923

ACTION – An inhibitor of β -lactamases for the treatment of β -lactam antibiotic-resistant bacterial infections in combination with β -lactam antibiotics. *In vitro*, compound inhibited AmpC β -lactamase from *Escherichia coli* and PCI β -lactamase from *Staphylococcus aureus* with IC₅₀ values of 0.08 and 2 μ M, respectively. In addition, it was shown to potentiate the *in vitro* antibacterial activity of amoxicillin when tested against a panel of resistant strains, MIC values of amoxicillin ranging from 32 μ g/ml to 256 μ g/ml when tested alone and from 4 μ g/ml to 16 μ g/ml when given in combination with the β -lactamase inhibitor. Other compounds from this series of boronic acid derivatives include the following:



Compound	R1	Formula
291504	4-(PhSO2)-2-thienyl	C ₁₆ H ₁₄ BNO ₆ S ₃
291505	3-[3-B(OH)2-PhNHSO2]-Ph	C ₁₈ H ₁₈ B ₂ N ₂ O ₈ S ₂

SOURCES – Università degli Studi di Modena, Modena (IT); Northwestern University, Evanston, IL (US).

REFERENCES

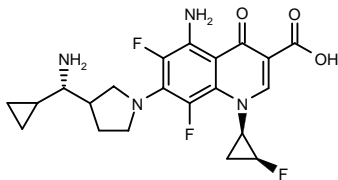
1. Shoichet, B.K. et al. (Northwestern University;Università degli Studi di Modena e Reggio Emilia) *Inhibitors of β -lactamases and uses therefor*. WO 0035904.

2. Tondi, D. et al. *Structure-based design and parallel synthesis of boronic acid inhibitors of AmpC β -lactamase*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1228.

ANTIBACTERIAL DRUGS

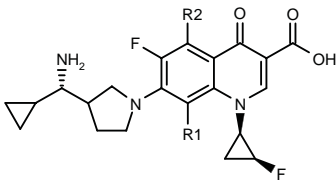
290741

5-Amino-7-[3-[(*S*)-amino(cyclopropyl)methyl]pyrrolidin-1-yl]-6,8-difluoro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C21 H23 F3 N4 O3; Mol wt: 436.4317

ACTION – Antibacterial agent with excellent activity against both Gram-positive and Gram-negative microorganisms. *In vitro*, compound exhibited MIC values of 0.003 μ g/ml or less against *Escherichia coli* NIHJ, *Shigella flexneri* 2A 5503, *Staphylococcus aureus* FDA 209P, *Staphylococcus epidermidis* 56500, *Streptococcus pyogenes* G-36 and *Streptococcus pneumoniae* J24, and was also highly active against a number of other strains. Other specifically claimed compounds from this series of cycloalkyl-substituted aminomethylpyrrolidine derivatives are:



Compound	R1	R2	Formula
290743	Me	NH2	C ₂₂ H ₂₆ F ₂ N ₄ O ₃
290747	OMe	H	C ₂₂ H ₂₅ F ₂ N ₃ O ₄

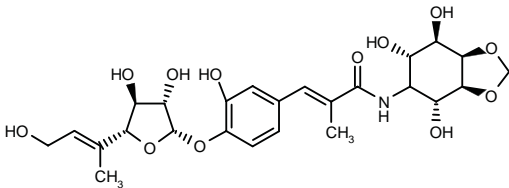
SOURCE – Daiichi Pharmaceutical.

REFERENCES

1. Takemura, M. et al. (Daiichi Pharmaceutical Co., Ltd.) *Cycloalkyl-substd. aminomethylpyrrolidine derivs*. WO 0031062.

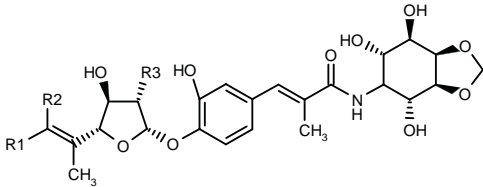
291000

3-[4-[(2*S*,3*S*,4*S*,5*R*)-3,4-Dihydroxy-5-[3-hydroxy-1-methyl-1(*E*)-propenyl]tetrahydrofuran-2-yloxy]-3-hydroxyphenyl]-2-methyl-*N*-[(3*aS*,4*R*,6*S*,7*R*,7*aR*)-4,6,7-trihydroxyhexahydro-1,3-benzodioxol-5-yl]-2(*E*)-propenamide

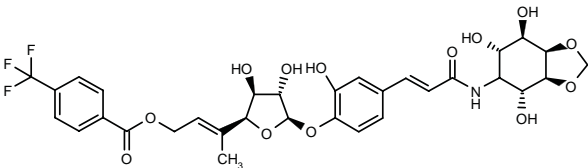


C25 H33 N O12; Mol wt: 539.5307

ACTION – Antibacterial and antiprotozoal agent, a representative compound from a series of hygromycin A derivatives, wherein the following are also specifically claimed:



Compound	R1	R2	R3	Formula
291008	3-Pyr-OCH2	H	OH	C ₃₀ H ₃₆ N ₂ O ₁₂
291009	4-Cl-2-(PhCO)-PhOCH2	H	OH	C ₃₈ H ₄₀ ClNO ₁₃
291010	H	2-F-PhOCH2	OH	C ₃₁ H ₃₆ FNO ₁₂
291011	Me	2-Cl-PhOCH2	OH	C ₃₂ H ₃₈ ClNO ₁₂
291012	2-Cl-4-F-PhOCH2	Me	H	C ₃₂ H ₃₇ ClFNO ₁₁



291007: C32 H34 F3 N O13

SOURCE – Pfizer.

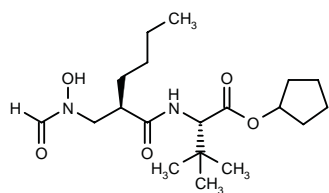
REFERENCES

1. Hayward, M.M. (Pfizer Products Inc.) *Hygromycin A derivs. as antibacterial agents*. WO 0032616.

291626

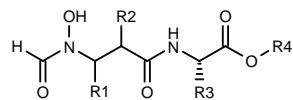
2(S)-[2(R)-(N-Formyl-N-hydroxyaminomethyl)hexan-amido]-3,3-dimethylbutyric acid cyclopentyl ester

N-[2(R)-(N-Formyl-N-hydroxyaminomethyl)hexanoyl]-L-tert-leucine cyclopentyl ester



C19 H34 N2 O5; Mol wt: 370.4866

ACTION – Antibacterial agent that is believed to act by inhibiting the bacterial polypeptide deformylase (PDF). The compound was active against *Escherichia coli* DH5α and *Staphylococcus capitis* ATCC 35661 strains, with respective MIC values of 50 and 12.5 μM. Other exemplified N-formyl hydroxylamine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
291627	H	CH2Ph	CH2Ph	cyclopentyl	C ₂₅ H ₃₀ N ₂ O ₅
291628	Me	(R)-i-Bu	CH2Ph	cyclopentyl	C ₂₃ H ₃₄ N ₂ O ₅
291629	H	(R)-Bu	CH2Ph	cyclopentyl	C ₂₂ H ₃₂ N ₂ O ₅
291630	H	(R)-Bu	t-Bu	Me	C ₁₅ H ₂₈ N ₂ O ₅
291631	H	Bu	i-Pr	cyclopentyl	C ₁₈ H ₃₂ N ₂ O ₅

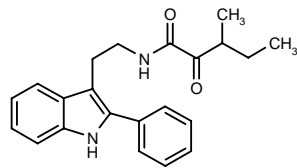
SOURCE – British Biotech.

REFERENCES

1. Hunter, M.G. et al. (British Biotech Pharmaceuticals Ltd.) *N-Formyl hydroxylamine derivs. as antibacterial agents*. WO 0035440.

291943

3-Methyl-2-oxo-N-[2-(2-phenyl-1H-indol-3-yl)ethyl]-pentanamide



C22 H24 N2 O2; Mol wt: 348.4436

ACTION – Antibacterial agent, a nematophin derivative active against *Staphylococcus aureus* 853 (MIC = 0.03 μg/ml or less) and methicillin-resistant *S. aureus* (MIC = 0.06 μg/ml); it also showed weak activity against *Bacillus subtilis* (MIC = 8 μg/ml).

SOURCE – Glaxo Wellcome.

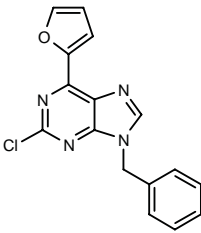
REFERENCES

1. Kennedy, G. et al. *Studies on the novel anti-staphylococcal compound nematophin*. Bioorg Med Chem Lett 2000, 10(15): 1751.

ANTIMYCOBACTERIAL AGENTS

290371

9-Benzyl-2-chloro-6-(2-furyl)-9H-purine



C16 H11 Cl N4 O; Mol wt: 310.7429

ACTION – Antimycobacterial agent active against *Mycobacterium tuberculosis* (MIC = 0.78 μg/ml), with potency comparable to rifampicin (MIC = 0.25 μg/ml); compound exhibited low cytotoxicity in Vero cells (IC₅₀ = 8.1 μg/ml), giving a selectivity index of 10.4.

SOURCE – Universitetet i Oslo, Oslo (NO).

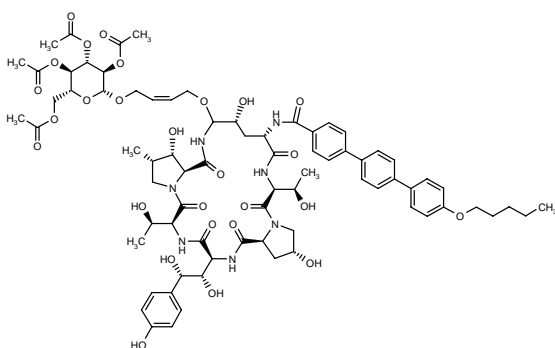
REFERENCES

1. Bakkestuen, A.K. et al. *9-Benzylpurines with inhibitory activity against Mycobacterium tuberculosis*. Bioorg Med Chem Lett 2000, 10(11): 1207.
2. Langli, G. et al. *Regiochemistry in Stille couplings of 2,6-dihalopurines*. Tetrahedron 1996, 52(15): 5625.

ANTIFUNGAL AGENTS

291612

(2*R*,5*S*,9*R*,14*aS*,15*S*,16*S*,20*S*,23*S*,25*aS*)-23-[1(*S*),2(*R*)-Dihydroxy-2-(4-hydroxyphenyl)ethyl]-2,11,15-trihydroxy-6-[1(*R*)-hydroxyethyl]-20-[1(*S*)-hydroxyethyl]-16-methyl-9-[4''-(pentyloxy)-*p*-terphenyl-4-ylcarboxamido]-12-[4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-2(*Z*)-butenyloxy]perhydropyrrolo[2,1-*c*:2',1'-*I*]-[1,4,7,10,13,16]hexaazacycloheneicosine-5,8,14,19,22,25-hexaone



C76 H97 N7 O27; Mol wt: 1540.6240

ACTION – Antifungal and antiparasitic compound from a series of semisynthetic cyclic peptides. Representative compounds of the invention displayed activity against at least one of the following fungi: *Candida albicans*, *Candida parapsilosis*, *Cryptococcus neoformans*, *Histoplasma* spp. and *Aspergillus fumigatus*, and inhibit the growth of *Pneumocystis carinii* and other protozoans such as *Plasmodium* spp., *Leishmania* spp., *Trypanosoma* spp., *Cryptosporidium* spp., *Isospora* spp., *Cyclospora* spp., *Trichomonas* spp., *Microsporidiosis* spp. and the like.

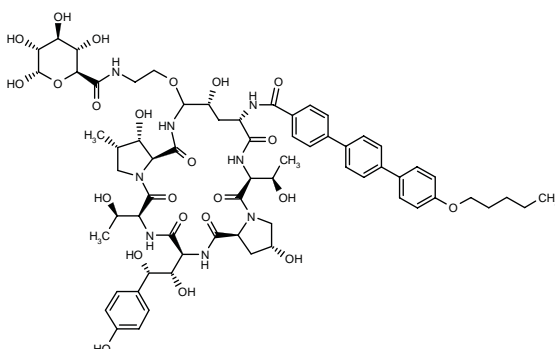
SOURCE – Lilly.

REFERENCES

1. Rodriguez, J.M. and Jamison, J.A. (Eli Lilly and Company) *Cyclic peptide antifungal agents*. WO 0035944.

291613

(2*R*,5*S*,9*R*,14*aS*,15*S*,16*S*,20*S*,23*S*,25*aS*)-23-[1(*S*),2(*R*)-Dihydroxy-2-(4-hydroxyphenyl)ethyl]-12-[2-(α-D-galactopyranosyluronamido)ethoxy]-2,11,15-trihydroxy-6-[1(*R*)-hydroxyethyl]-20-[1(*S*)-hydroxyethyl]-16-methyl-9-[4''-(pentyloxy)-*p*-terphenyl-4-ylcarboxamido]perhydropyrrolo[2,1-*c*:2',1'-*I*]-[1,4,7,10,13,16]hexaazacycloheneicosine-5,8,14,19,22,25-hexaone



C66 H86 N8 O23; Mol wt: 1359.4380

ACTION – Antifungal and antiparasitic compound from a series of semisynthetic cyclic peptides. Representative compounds of the invention displayed activity against at least one of the following fungi: *Candida albicans*, *Candida parapsilosis*, *Cryptococcus neoformans*, *Histoplasma* spp. and *Aspergillus fumigatus*, and inhibit the growth of *Pneumocystis carinii* and other protozoans such as *Plasmodium* spp., *Leishmania* spp., *Trypanosoma* spp., *Cryptosporidium* spp., *Isospora* spp., *Cyclospora* spp., *Trichomonas* spp., *Microsporidiosis* spp. and the like.

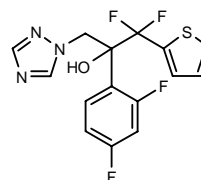
SOURCE – Lilly.

REFERENCES

1. Rodriguez, J.M. et al. (Eli Lilly and Company) *Cyclic peptide antifungal agents having a sugar substituent*. WO 0035945.

291705

(+)-2-(2,4-Difluorophenyl)-1,1-difluoro-1-(2-thienyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol



C15 H11 F4 N3 O S; Mol wt: 357.3299

Colorless powder, m.p. 97-8 °C; [α]_D²⁴ +7.99° (c 0.1 MeOH).

ACTION – Antifungal agent, a 1,2,4-triazole derivative with strong activity against yeasts and filamentous fungi. In particular, compound exhibited activity superior to fluconazole and itraconazole against *Candida albicans* (MIC = 0.016 µg/ml or less, 0.5 and 0.063 µg/ml, respectively), *Candida krusei* (MIC = 0.063, 64 and 0.5 µg/ml, respectively), *Trichophyton mentagrophytes* (MIC = 0.063, 64 and 0.5 µg/ml, respectively) and *Trichophyton rubrum* (MIC = 0.016 µg/ml or less, 64 and 0.25 µg/ml, respectively). Compound exhibited equivalent activity to itraconazole against *Aspergillus flavus* and *Aspergillus fumigatus* (MIC = 0.5 µg/ml).

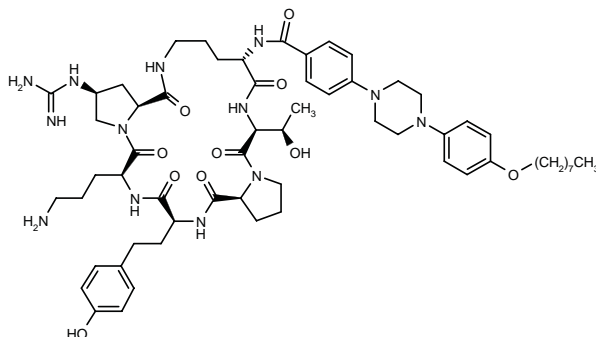
SOURCE – SSP.

REFERENCES

1. Eto, H. et al. *New antifungal 1,2,4-triazoles with difluoro(heteroaryl)methyl moiety*. Chem Pharm Bull 2000, 48(7): 982.

292087

N-[(6*S*,9*S*,14*aS*,16*S*,20*S*,23*S*,25*aS*)-20-(3-Aminopropyl)-16-guanidino-6-[1(*R*)-hydroxyethyl]-23-[2-(4-hydroxyphenyl)ethyl]-5,8,14,19,22,25-hexaoxotetracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'-*l*][1,4,7,10,13,16]hexaazacycloheneicosin-9-yl]-4-[4-[4-(octyloxy)phenyl]piperazin-1-yl]benzamide



C60 H87 N13 O10; Mol wt: 1150.4280

ACTION – Antifungal agent with potent activity against *Candida albicans* strains ATCC 62376 and ATCC 38247 (sensitive and resistant to polyenes, respectively) and *Candida glabrata* strain ATCC 15545 (MIC = 0.2 µg/ml against all strains). *In vivo*, in an acute *C. albicans* murine infection model, compound was 5-fold more active than amphotericin B.

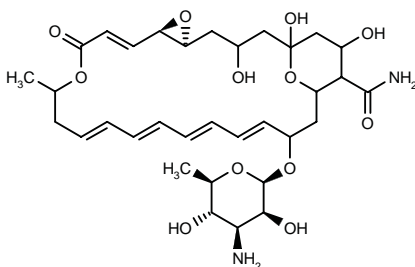
SOURCES – Abbott; Chiron; Pharmacia; Scriptgen; Tularik.

REFERENCES

1. Klein, L.L. et al. *Total synthesis and antifungal evaluation of cyclic aminohexapeptides*. *Bioorg Med Chem Lett* 2000, 8(7): 1677.

AB-400**291266**

(5*S*,6*R*)-21-(4-Amino-3,6-dideoxy-β-D-mannopyranosyloxy)-5,6-epoxy-1,3,25-trihydroxy-11-methyl-9-oxo-10,27-dioxabicyclo[21.3.1]heptacos-6,13,15,17,19-pentaen-24-carboxamide



C33 H48 N2 O12; Mol wt: 664.7442

ACTION – Antifungal agent, a macrolide extracted from a culture broth of *Streptomyces costae* proven active against *Candida albicans* and *Candida tropicalis*, with MIC values of 18 and 4.6 µM, respectively, compared with 0.86 and 1.7 µM, respectively, for amphotericin B, and 3.3 µM against both species for nystatin.

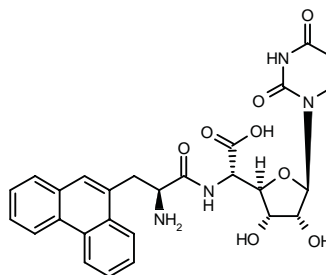
SOURCE – Antibioticos.

REFERENCES

1. Salto Maldonado, F. et al. (Antibioticos SA) *A process for the preparation of polyene antifungal antibiotics and new tetraene antifungal antibiotic*. GB 2106498.
2. Cañedo, L.M. et al. *AB-400, a new tetraene macrolide isolated from Streptomyces costae*. *J Antibiot* 2000, 53(6): 623.

KFC-431**291277**

5(*R*)-[2(*S*)-Amino-3-(9-phenanthryl)propionamido]-1,5-dideoxy-1-(uracil-1-yl)-β-D-allofuranuronic acid



C27 H26 N4 O8; Mol wt: 534.5224

ACTION – Chitin synthase inhibitor, an analogue of the natural product nikkomycin with comparable enzyme-inhibitory activity (IC₅₀ = 0.31 and 0.393 µg/ml, respectively), potentially useful as an antifungal agent.

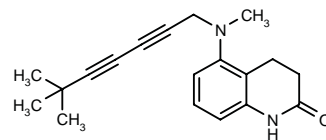
SOURCE – Kyorin.

REFERENCES

1. Obi, K. et al. *Novel nikkomycin analogues: Inhibitors of the fungal cell wall biosynthesis enzyme chitin synthase*. *Bioorg Med Chem Lett* 2000, 10(13): 1451.

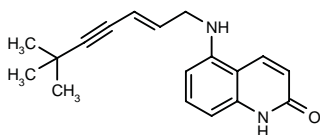
RO-09-3024**291278**

5-[*N*-(6,6-Dimethyl-2,4-heptadiynyl)-*N*-methylamino]-1,2,3,4-tetrahydroquinolin-2-one



C19 H22 N2 O; Mol wt: 294.3958

ACTION – Antifungal agent, a chitin synthase 1 inhibitor (IC_{50} = 0.14 nM) derived from chemical modification of **Ro-41-0986**, with strong antifungal activity against a wide range of *Candida species* including *Candida albicans* (IC_{50} = 0.09-0.10 µg/ml), azole-resistant *C. albicans* (IC_{50} = 0.17 µg/ml), *Candida glabrata* (IC_{50} = 0.47 µg/ml), *Candida tropicalis* (IC_{50} = 0.07 µg/ml), *Candida krusei* (IC_{50} = 0.31 µg/ml) and *Candida parapsilosis* (IC_{50} = 0.5 µg/ml); it was weakly active against *Aspergillus fumigatus* (IC_{50} = 43 µg/ml) and inactive against *Cryptococcus neoformans* (IC_{50} > 200 µg/ml). In comparison with nikkomycin Z, it showed a significantly better antifungal spectrum. Despite its high *in vitro* activity, however, compound exhibited only weak *in vivo* efficacy in a systemic candidiasis model in mice, probably due to its rapid metabolism, strong serum protein binding and low water solubility.



Ro-41-0986 [291490]: C₁₈ H₂₀ N₂ O

SOURCE – Nippon Roche.

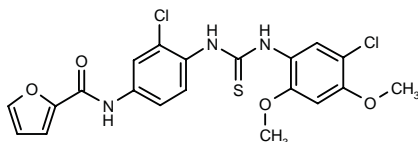
REFERENCES

1. Masabuchi, K. et al. *Synthesis and structure-activity relationships of novel fungal chitin synthase inhibitors*. Bioorg Med Chem Lett 2000, 10(13): 1459.

ANTIVIRAL DRUGS

291289

N-[4-[*N'*-(5-Chloro-2,4-dimethoxyphenyl)thioureido]-3-chlorophenyl]furan-2-carboxamide



C₂₀ H₁₇ Cl₂ N₃ O₄ S; Mol wt: 466.3433

ACTION – Antiviral agent for the treatment of diseases associated with herpesviruses including human cytomegalovirus (HCMV), herpes simplex viruses (HSV), Epstein-Barr virus, varicella-zoster virus (VZV), human herpesviruses-6 and -7 and Kaposi herpesvirus. *In vitro*, compound exhibited IC_{50} values of 0.4, 0.5 and 1.9 µg/ml against HCMV, HSV-1 and VZV, respectively. A representative compound from a series of heterocyclic carboxamide-containing thiourea derivatives.

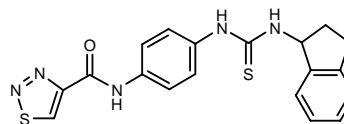
SOURCE – American Home Products.

REFERENCES

1. Bloom, J.D. et al. (American Home Products Corp.) *Heterocyclic carboxamide-containing thiourea inhibitors of herpes viruses containing a substd. phenylenediamine group*. WO 0034261.

291290

N-[4-[*N'*-(Indan-1-yl)thioureido]phenyl]-1,2,3-thiadiazole-4-carboxamide



C₁₉ H₁₇ N₅ O S₂; Mol wt: 395.5093

ACTION – Antiviral agent for the treatment of diseases associated with herpesviruses including human cytomegalovirus (HCMV), herpes simplex viruses (HSV), Epstein-Barr virus, varicella-zoster virus (VZV), human herpesviruses-6 and -7 and Kaposi herpesvirus. *In vitro*, compound exhibited IC_{50} values of 0.02 and 0.5 µg/ml against HCMV and VZV, respectively, while it was inactive against HSV-1 (IC_{50} > 10 µg/ml). A representative compound from a series of thiourea derivatives.

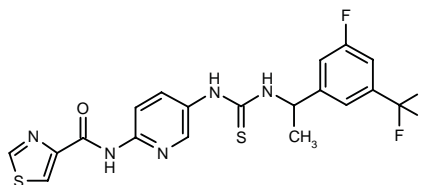
SOURCE – American Home Products.

REFERENCES

1. Bloom, J.D. et al. (American Home Products Corp.) *Thiourea inhibitors of herpes viruses*. WO 0034268.

291291

N-[5-[*N'*-[1-[3-Fluoro-5-(trifluoromethyl)phenyl]ethyl]-thioureido]pyridin-2-yl]thiazole-4-carboxamide



C₁₉ H₁₅ F₄ N₅ O S₂; Mol wt: 469.4855

ACTION – Antiviral agent for the treatment of diseases associated with herpesviruses including human cytomegalovirus (HCMV), herpes simplex viruses (HSV), Epstein-Barr virus, varicella-zoster virus (VZV), human herpesviruses-6 and -7 and Kaposi herpesvirus. *In vitro*, compound exhibited IC_{50} values of 0.0013 and 3.4 µg/ml against HCMV and VZV, respectively. A representative compound from a series of thiourea derivatives.

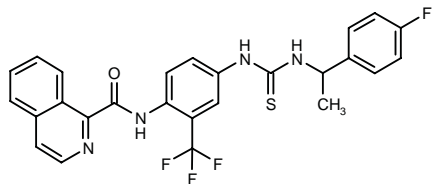
SOURCE – American Home Products.

REFERENCES

1. Bloom, J.D. et al. (American Home Products Corp.) *Thiourea inhibitors of herpes viruses*. WO 0034269.

291292

N-[4-[N'-[1-(4-Fluorophenyl)ethyl]thioureido]-2-(trifluoromethyl)phenyl]isoquinoline-1-carboxamide



C26 H20 F4 N4 O S; Mol wt: 512.5290

ACTION – Antiviral agent for the treatment of diseases associated with herpesviruses including human cytomegalovirus (HCMV), herpes simplex viruses (HSV), Epstein-Barr virus, varicella-zoster virus (VZV), human herpesviruses-6 and -7 and Kaposi herpesvirus. *In vitro*, compound exhibited IC₅₀ values of 1.8, 1.9 and 0.02 µg/ml against HCMV, HSV-1 and VZV, respectively. A representative compound from a series of thiourea derivatives.

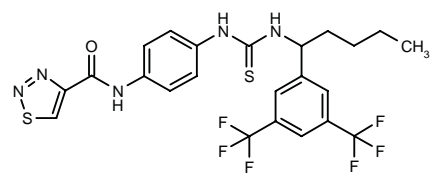
SOURCE – American Home Products.

REFERENCES

1. Bloom, J.D. et al. (American Home Products Corp.) *Thiourea inhibitors of herpes viruses*. WO 0034238.

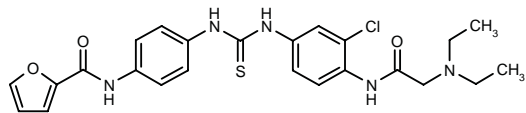
291293

N-[4-[N'-[1-[3,5-Bis(trifluoromethyl)phenyl]pentyl]-thioureido]phenyl]-1,2,3-thiadiazole-4-carboxamide



C23 H21 F6 N5 O S2; Mol wt: 561.5729

ACTION – Antiviral agent for the treatment of diseases associated with herpesviruses including human cytomegalovirus (HCMV), herpes simplex viruses (HSV), Epstein-Barr virus, varicella-zoster virus (VZV), human herpesviruses-6 and -7 and Kaposi herpesvirus. *In vitro*, compound exhibited IC₅₀ values of 0.00001 and 0.5 µg/ml against HCMV and VZV, respectively. A representative compound from a series of heterocyclic carboxamide-containing thiourea derivatives, wherein the following is also included:



291294: C24 H26 Cl N5 O3 S

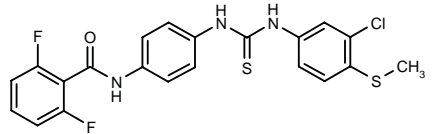
SOURCE – American Home Products.

REFERENCES

1. Bloom, J.D. et al. (American Home Products Corp.) *α-Methylbenzyl-containing thiourea inhibitors of herpes viruses containing a phenylenediamine group*. WO 0034260.

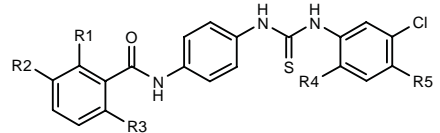
291295

N-[4-[N'-(3-Chloro-4-methylthiophenyl)thioureido]phenyl]-2,6-difluorobenzamide



C21 H16 Cl F2 N3 O S2; Mol wt: 463.9584

ACTION – Antiviral agent for the treatment of diseases associated with herpesviruses including human cytomegalovirus (HCMV), herpes simplex virus (HSV), Epstein-Barr virus, varicella-zoster virus (VZV), human herpesviruses-6 and -7 and Kaposi herpesvirus. *In vitro*, compound exhibited IC₅₀ values of 0.3, 0.085 and 1.3 µg/ml against HCMV, HSV-1 and VZV, respectively. A representative compound from a series of α-methylbenzyl-containing thiourea derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
291296	H	OAc	H	OMe	OMe	C ₂₄ H ₂₂ ClN ₃ O ₅ S
291297	F	H	F	H	1-Me-3-pyrrolidinyl-N(Me)	C ₂₆ H ₂₆ ClF ₂ N ₅ OS

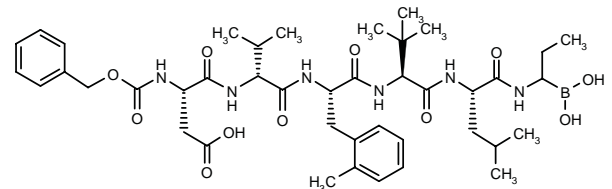
SOURCE – American Home Products.

REFERENCES

1. Bloom, J.D. et al. (American Home Products Corp.) *α-Methylbenzyl-containing thiourea inhibitors of herpes viruses containing a phenylenediamine group*. WO 0034260.

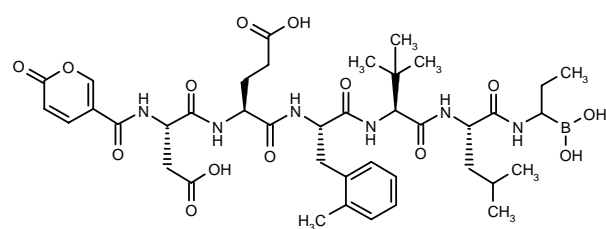
292052^{2,3}

Benzyloxycarbonyl-L-aspartyl-L-valyl-L-3-(2-methylphenyl)alanyl-L-(3-methyl)valyl-L-leucine N-(1-borono-propyl)amide



C42 H63 B N6 O11; Mol wt: 838.8017

ACTION – Potent inhibitor of hepatitis C virus NS3 protease. Another related aminoboronic acid with potential in the treatment of hepatitis C virus (HCV) infection is:



292053:^{1,3} C40 H57 B N6 O14

SOURCE – Roche.

REFERENCES

1. Attwood, M.R. et al. (F. Hoffmann-La Roche AG) *Antiviral peptide derivs.* GB 2337262.

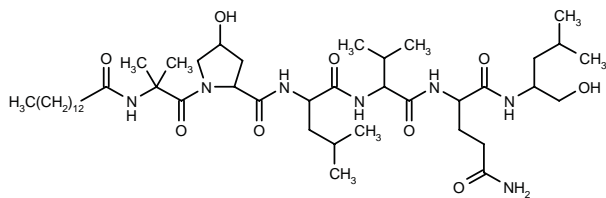
2. Attwood, M.R. et al. (F. Hoffmann-La Roche AG) *Antiviral peptide derivs.* JP 2000508344, WO 9822496.

3. Dunsdon, R.M. et al. *Solid phase synthesis of aminoboronic acids: Potent inhibitors of the hepatitis C virus NS3 proteinase.* Bioorg Med Chem Lett 2000, 10(14): 1577.

HALOVIR A

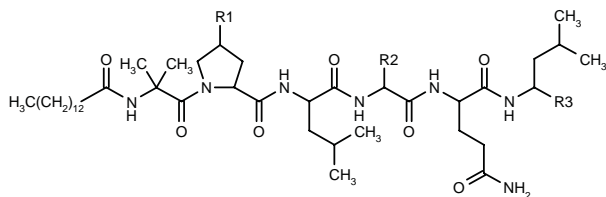
291520

*N*¹-[1-(Hydroxymethyl)-3-methylbutyl]-2-[2-[2-[4-hydroxy-1-[2-methyl-2-(tetradecanoylamino)propanoyl]pyrrolidin-2-ylcarboxamido]-4-methylpentanoylamino]-3-methylbutanoylamino]pentanediamide



C45 H83 N7 O9; Mol wt: 866.1907

ACTION – Antiviral agent, a member of a family of hexapeptides and hexapeptide-like compounds isolated from the fermentation of the marine fungus *Scytalidium* sp. CNL240, particularly active against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) and cytomegalovirus (CMV) infections. Halovir A was highly effective in *in vitro* assays, inactivating HSV-1 in Vero cells. Other compounds from the same source are:



Compound	R1	R2	R3	Formula
Halovir B [291521]	OH	Me	CH2OH	C ₄₃ H ₇₉ N ₇ O ₉
Halovir C [291522]	H	i-Pr	CH2OH	C ₄₅ H ₈₃ N ₇ O ₈
Halovir D [291523]	OAc	i-Pr	CH2OAc	C ₄₉ H ₈₇ N ₇ O ₁₁
Halovir E [291524]	OH	Me	CO2Me	C ₄₄ H ₇₉ N ₇ O ₁₀

SOURCE – University of California, Oakland, Oakland, CA (US).

REFERENCES

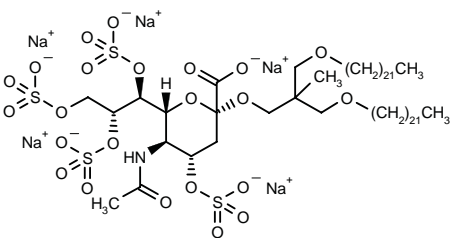
1. Fenical, W. et al. (University of California, Oakland) *Halovir, an antiviral marine natural product, and derivs. thereof.* WO 0035943.

NMSO3

288307

5-Acetamido-2-*O*-[2,2-bis(docosyloxymethyl)propyl]-3,5-dideoxy-4,7,8,9-tetra-*O*-sulfo-D-*glycero*-D-*galacto*-2-nonulopyranosuronic acid pentasodium salt

N-Acetyl-2-*O*-[3-(docosyloxy)-2-(docosyloxymethyl)-2-methylpropyl]-α-neuraminic acid 4,7,8,9-tetrakis(hydrogen sulfate) pentasodium salt



C60 H112 N Na5 O23 S4; Mol wt: 1458.7430

ACTION – Antiviral agent active against respiratory syncytial virus (RSV) and other myxovirus infections in cell culture. Compound was able to inhibit the replication of the Long strain of RSV in HEp-2 cells (EC₅₀ = 0.2-0.32 μM) and showed potent activity against other laboratory strains and clinical isolates of RSV, with an average EC₅₀ of 0.23 μM. In comparison to ribavirin, compound was at least 20-fold more active against the Long strain (EC₅₀ = 10.5-11.2 μM for ribavirin). It showed low cytotoxicity against HEp-2, MDCK, HMV-2 and Vero cells, with a CC₅₀ > 682 μM, providing a selectivity index (SI) > 2,978 versus 6 for ribavirin. Compound also showed minor activity against influenza virus A (EC₅₀ = 17.8-23.8 μM) but was inactive (up to > 100 μM) against influenza virus B, parainfluenza virus type 2 and canine distemper virus. It inhibited RSV infection of HEp-2 cells when added between 0 and 1.5 h after virus infection and both the binding and penetration of RSV into the cell. *In vivo*, compound exhibited both prophylactic and therapeutic efficacy when given at a dose of 100 mg/kg/day i.p. every 24 h from 1 day before to 3 days after intranasal infection with RSV, inducing a significant reduction in RSV titers in the lungs.

SOURCE – Nissin Food Products.

REFERENCES

1. Fujita, S. et al. (Nissin Food Products Co., Ltd.) *Novel cpds. having antiviral activity.* CA 2255070, EP 0957107, WO 9743296.

2. Kimura, K. et al. *Antiviral activity of NMSO3 against respiratory syncytial virus infection in vitro and in vivo.* Antivir Res 2000, 47(1): 41.

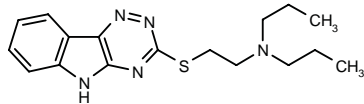
3. Shigeta, S. et al. *NMSO3, a potent inhibitor of respiratory syncytial virus (RSV) infection in vitro and in vivo.* Antivir Res 2000, 46(1): Abst 56.

VP-32947

290961

N-Propyl-N-[2-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-ylsulfanyl)-ethyl]-1-propanamine

3-[2-(*N,N*-Dipropylamino)ethylsulfanyl]-5*H*-1,2,4-triazino[5,6-*b*]indole



C17 H23 N5 S; Mol wt: 329.4697

ACTION – Antiviral agent, a Pestivirus-specific agent effective against all four species of cytopathic and noncytopathic Pestivirus including bovine viral diarrhea virus 1 (BVDV-1; IC₅₀ ~ 20 nM in MDBK cells), BVDV-2, border disease virus (strain 31) and classical swine fever virus (strain C); compound was not active against other unrelated viruses such as dengue virus (type 2), yellow fever virus, influenza A virus, respiratory syncytial virus, Coxsackievirus and herpes simplex virus type 2. The mechanism by which it inhibits virus replication involves inhibition of viral RNA synthesis, targeting the NS5B protein. Given the similarities between Pestivirus and hepatitis C virus (HCV), compound may serve as a lead in the development of new HCV antiviral drugs.

SOURCE – ViroPharma.

REFERENCES

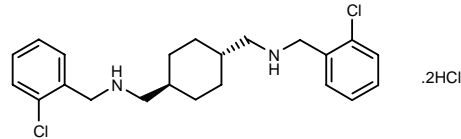
1. Pevear, D.C. et al. (ViroPharma, Inc.) *Methods for preventing and treating pestivirus infection and associated diseases*. WO 9836752.
2. Baginski, S.G. et al. *Mechanism of action of a pestivirus antiviral compound*. Proc Natl Acad Sci USA 2000, 97(14): 7981.

AIDS MEDICINES

AY-9944

269252

trans-*N,N'*-Bis(2-chlorobenzyl)-1,4-cyclohexanedi-methanamine dihydrochloride



C22 H28 Cl2 N2 . 2HCl; Mol wt: 464.3050

ACTION – Cationic amphiphilic inhibitor of sterol synthesis found to help restore cell survival and cytokine profiles of peripheral blood mononuclear cells (PBMCs) from AIDS patients *in vitro*. Following 2 weeks' exposure to compound, the percentage of dead CD4+ cells in HIV-1-infected PBMC cultures was comparable to that observed in controls and about 3-5-fold lower than in HIV-1-infected cultures not treated with compound; it also stimulated by 2-12-fold IL-12 and interferon gamma production. In addition, the compound stimulated the expression of β -chemokines, increasing by 7-40-fold mean levels of MIP-1 α , MIP-1 β and RANTES in naturally HIV-1-infected PBMCs. Although it has no direct antiviral effect, it is considered to have potential as a therapeutic agent for HIV-infected patients to enhance the level of resistance to HIV and opportunistic infections.

SOURCE – Université Pierre et Marie Curie - Paris 6, Paris (FR).

REFERENCES

1. Achour, A. *Increased β -chemokine production in peripheral blood mononuclear cells derived from HIV-1-infected individuals by a cationic amphiphilic drug (AY 9944) in vitro*. AIDS 2000, 14(10): 1454.
2. Achour, A. et al. *Restoration of immune response by a cationic amphiphilic drug (AY 9944) in vitro: A new approach to chemotherapy against human immunodeficiency virus type 1*. Antimicrob Agents Chemother 1998, 42(10): 2482.

HL-9

291495

L-Arginyl-L-alanyl-L-tryptophyl-L-valyl-L-alanyl-L-tryptophyl-L-arginyl-L-asparaginyll-L-arginine

C55 H83 N21 O11; Mol wt: 1214.3970

ACTION – Anti-HIV agent, a 9-amino-acid fragment of human lysozyme with strong anti-HIV activity against a wide spectrum of primary isolates, laboratory and resistant strains, with IC₅₀ values ranging from 55 to 68 nM. Compound also inhibited human herpesvirus type 8 (HHV8) proliferation in HHV8-infected cells from AIDS patients with Kaposi's sarcoma. It is devoid of cytotoxicity at pharmacologically active concentrations. Another lysozyme fragment is:

L-Arginyl-L-valyl-L-valyl-L-arginyl-L-aspartyl-L-prolyl-L-glutaminyll-glycyl-L-isoleucyl-L-arginyl-L-alanyl-L-tryptophyl-L-valyl-L-alanyl-L-tryptophyl-L-arginyl-L-asparaginyll-L-arginine

HL-18 [291494]; C99 H159 N37 O23

SOURCES – American BioScience; New York Medical College, Valhalla, NY (US).

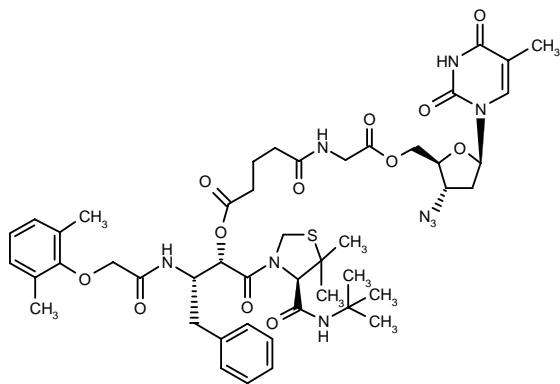
REFERENCES

1. Huang, P. et al. *Identification, characterization and synthesis of lysozyme mimetics with potent anti-HIV activity*. 13th Int AIDS Conf (July 9-14, Durban) 2000, Abstr TuOrA405.

KNI-1039

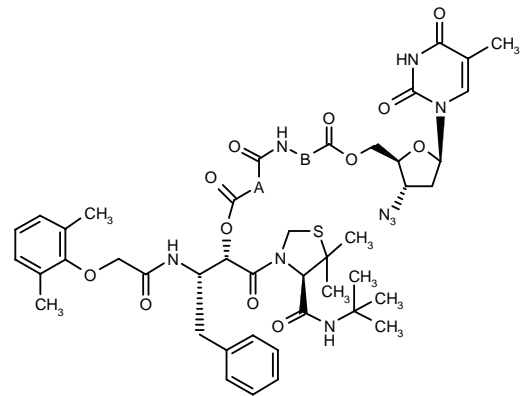
290364

3'-Azido-5'-O-[2-[5-[1(S)-[4(R)-(N-tert-butylcarbamoyl)-5,5-dimethylthiazolidin-3-ylcarbonyl]-2(S)-[2-(2,6-dimethylphenoxy)acetamido]-3-phenylpropoxy]-5-oxopentanamido]acetyl]-3'-deoxythymidine



C47 H61 N9 O12 S; Mol wt: 976.1159

ACTION – Prodrug-type anti-HIV agent, a peptidomimetic HIV protease inhibitor (KNI-727) conjugated with a nucleoside reverse transcriptase inhibitor (zidovudine) via a spontaneously cleavable linker. This hybrid-type compound penetrates into the cell membrane and disintegrates spontaneously to generate the two enzyme inhibitors, exhibiting strong synergistic anti-HIV activity (EC₅₀ = 0.1 nM) and low cytotoxicity (therapeutic index > 2,000); compound was 920- and 62-fold more potent than KNI-727 and zidovudine, respectively. Within this class of double drugs, the following are also described:



Compound	A	B	Formula
KNI-1038 [290523]	-(CH2)2-	-CH2-	C ₄₆ H ₅₉ N ₉ O ₁₂ S
KNI-1046 [290524]	-(CH2)2-	-(CH2)2-	C ₄₇ H ₆₁ N ₉ O ₁₂ S
KNI-1047 [290525]	-(CH2)3-	-(CH2)2-	C ₄₈ H ₆₃ N ₉ O ₁₂ S

SOURCES – Kyoto Pharmaceutical University, Kyoto (JP); Osaka Medical College, Osaka (JP).

REFERENCES

1. Matsumoto, H. et al. "Double-drugs" - A new class of prodrug form of an HIV protease inhibitor conjugated with a reverse transcriptase inhibitor by a spontaneously cleavable linker. Bioorg Med Chem Lett 2000, 10(11): 1227.

NFAT-KRAB

291468

Chimeric repression protein consisting of the DNA-binding domain of NFAT (nuclear factor of activated T-cells) and the Krnp-pel-associated Box (KRAB) domain of KOX-1, both of human origin

ACTION – Chimeric HIV-1 transcriptional repressor protein with potential as gene therapy for intracellular immunization against HIV. Transfection of HIV-1_{III_B}- and HIV-1_{BAL}-infected Jurkat cells with the chimeric transcriptional protein resulted in reduced production of the two HIV isolates, as well as the HIV-induced cytopathic effect. Ciclosporin, an NFAT inactivator, was able to reverse the HIV-suppressive effect.

SOURCE – Universität Freiburg, Freiburg (DE).

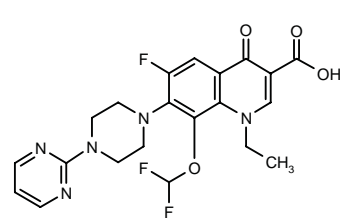
REFERENCES

1. Schneider, J. and Hahne, J. Repression of HIV-1 replication by the transcriptional repressor protein NFAT-KRAB. 13th Int AIDS Conf (July 9-14, Durban) 2000, Abst TuOrA406.

R-91650*

205745

8-(Difluoromethoxy)-1-ethyl-6-fluoro-4-oxo-7-[4-(2-pyrimidinyl)piperazin-1-yl]-1,4-dihydroquinoline-3-carboxylic acid



C21 H20 F3 N5 O4; Mol wt: 463.4140

ACTION – Anti-HIV agent proven to inhibit HIV-1 replication in acutely and chronically infected cells (IC₅₀ = 97.3-282.7 ng/ml) with low cytotoxicity. Compound also inhibited feline immunodeficiency virus (FIV) in FIV-infected peripheral blood mononuclear cells and feline kidney P-CrFK cells (IC₅₀ = 71.5 and 564.7 ng/ml, respectively). Its mechanism of action appeared to differ from that of reverse transcriptase inhibitors or protease inhibitors.

SOURCES – Sankyo; Ube.

REFERENCES

1. Ishimura, M. et al. (Ube Industries, Ltd.;Sankyo Co., Ltd.) Anti-HCMV agent. JP 1999302175, WO 9942106.

2. Kimura, T. and Katsube, T. (Ube Industries, Ltd.) Aminoquinolone derivs. as anti-HIV agents. EP 0572259, JP 1994116241, US 5519016, US 5688791.

3. Komai, T. et al. (Sankyo Co., Ltd.) Remedies for prevention of AIDS. JP 1997323932, WO 9727856.

4. Uchiyama, H. et al. (Sankyo Co., Ltd.;Ube Industries, Ltd.) TNF-production inhibitors. JP 1998130149.

5. Hagihara, M. et al. *Synthesis and anti-HIV activity of arylpiperazinyl fluoroquinolones: A new class of anti-HIV agents*. Bioorg Med Chem Lett 1999, 9(21): 3063.

6. Kashiwase, H. et al. *Investigation into the mode of action of R-91650, an arylpiperazinyl fluoroquinolone, on feline immunodeficiency virus replication inhibitory activity*. Arch Virol 2000, 145(5): 859.

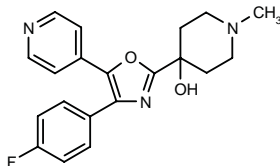
*Identified compound **205745** (see **203880**) Drug Data Rep 1994, 016(04): 0389.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

290366

4-[4-(4-Fluorophenyl)-5-(4-pyridyl)oxazol-2-yl]-1-methylpiperidin-4-ol



C20 H20 F N3 O2; Mol wt: 353.3950

ACTION – Potent inhibitor of p38 MAP kinase ($IC_{50} = 0.35 \mu M$ against p38 α) with high selectivity over other kinases including p38 β 2, JNK2 ($IC_{50} = 2.41$ and $8.1 \mu M$, respectively), as well as p38 δ , JNK1 and PKC α ($IC_{50} > 10 \mu M$). Compound inhibited TNF- α release both *in vitro* ($IC_{50} = 0.18 \mu M$) and *in vivo* in mice (50% inhibition at 10 mg/kg p.o.). It showed a good pharmacokinetic profile, with 65% oral bioavailability, and exhibited good antiinflammatory activity in the adjuvant-induced arthritis model in rats; it also strongly inhibited paw swelling in the collagen-induced arthritis model in rats ($ED_{50} = 10$ mg/kg/day p.o.). Due to its favorable efficacy and toxicity profile and its lack of inhibitory activity against cyclooxygenase type 1 (COX-1) and human cytochrome P-450 enzymes, compound is considered a promising development candidate for the treatment of rheumatoid arthritis.

SOURCE – Novartis.

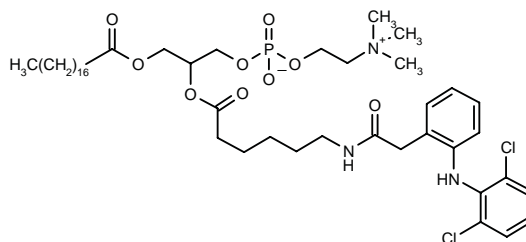
REFERENCES

1. Revesz, L. et al. *SAR of 4-hydroxypiperidine and hydroxyalkyl substituted heterocycles as novel p38 MAP kinase inhibitors*. Bioorg Med Chem Lett 2000, 10(11): 1261.

290677

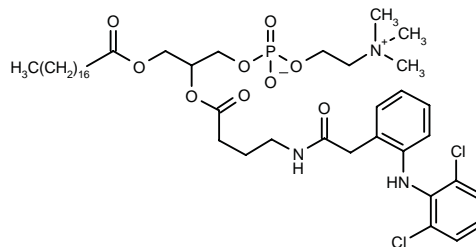
2-[6-[2-[2-(2,6-Dichlorophenylamino)phenyl]acetamido]hexanoyloxy]-3-(octadecanoyloxy)propyl 2-(trimethylammonium)ethyl phosphate

1-Stearoyl-2-[6-[2-[2-(2,6-dichlorophenylamino)phenyl]acetamido]hexanoyl]-*sn*-glycero-3-phosphatidylcholine



C46 H74 Cl2 N3 O9 P; Mol wt: 914.9826

ACTION – Diclofenac prodrug useful as an antiinflammatory agent, a representative compound from a series of phospholipid derivatives of nonsteroidal antiinflammatory drugs (NSAIDs) that act as prodrugs of NSAIDs; these compounds are designed to be cleaved by phospholipases such as PLA₂ that are specifically elevated at disease sites, thus resulting in accumulation of the active drug at the site of the disease while only low levels of prodrug cleavage occur in healthy tissue. Compound exhibited at 30 mg/kg p.o. comparable antiinflammatory activity to diclofenac at 10 mg/kg p.o. in the carrageenan-induced paw edema test in rats, and it also showed significant neuroprotective activity in a global forebrain ischemia model in gerbils at 30 mg/kg p.o., while diclofenac at 10 mg/kg p.o. exhibited weak activity. In addition, it exhibited greatly reduced subchronic toxicity in rats at 30 mg/kg/day p.o. x 14 days compared to diclofenac at 10 mg/kg p.o., as measured by body weight changes, and was found to be clearly less ulcerogenic in these animals. Another exemplified prodrug is:



290678: C44 H70 Cl2 N3 O9 P

SOURCE – D-Pharm.

REFERENCES

1. Kozak, A. and Shapiro, I. (D-Pharm Ltd.) *Phospholipid derivs. of non-steroidal anti-inflammatory drugs*. WO 0031083.

5. Hagihara, M. et al. *Synthesis and anti-HIV activity of arylpiperazinyl fluoroquinolones: A new class of anti-HIV agents*. Bioorg Med Chem Lett 1999, 9(21): 3063.

6. Kashiwase, H. et al. *Investigation into the mode of action of R-91650, an arylpiperazinyl fluoroquinolone, on feline immunodeficiency virus replication inhibitory activity*. Arch Virol 2000, 145(5): 859.

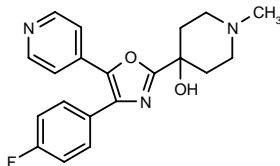
*Identified compound **205745** (see **203880**) Drug Data Rep 1994, 016(04): 0389.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

290366

4-[4-(4-Fluorophenyl)-5-(4-pyridyl)oxazol-2-yl]-1-methylpiperidin-4-ol



C20 H20 F N3 O2; Mol wt: 353.3950

ACTION – Potent inhibitor of p38 MAP kinase ($IC_{50} = 0.35 \mu M$ against p38 α) with high selectivity over other kinases including p38 β 2, JNK2 ($IC_{50} = 2.41$ and $8.1 \mu M$, respectively), as well as p38 δ , JNK1 and PKC α ($IC_{50} > 10 \mu M$). Compound inhibited TNF- α release both *in vitro* ($IC_{50} = 0.18 \mu M$) and *in vivo* in mice (50% inhibition at 10 mg/kg p.o.). It showed a good pharmacokinetic profile, with 65% oral bioavailability, and exhibited good antiinflammatory activity in the adjuvant-induced arthritis model in rats; it also strongly inhibited paw swelling in the collagen-induced arthritis model in rats ($ED_{50} = 10$ mg/kg/day p.o.). Due to its favorable efficacy and toxicity profile and its lack of inhibitory activity against cyclooxygenase type 1 (COX-1) and human cytochrome P-450 enzymes, compound is considered a promising development candidate for the treatment of rheumatoid arthritis.

SOURCE – Novartis.

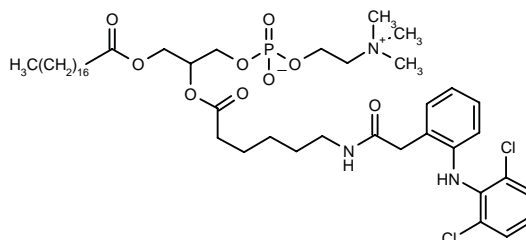
REFERENCES

1. Revesz, L. et al. *SAR of 4-hydroxypiperidine and hydroxyalkyl substituted heterocycles as novel p38 MAP kinase inhibitors*. Bioorg Med Chem Lett 2000, 10(11): 1261.

290677

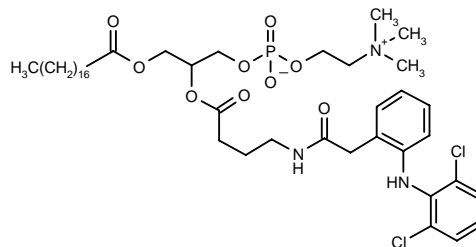
2-[6-[2-[2-(2,6-Dichlorophenylamino)phenyl]acetamido]hexanoyloxy]-3-(octadecanoyloxy)propyl 2-(trimethylammonium)ethyl phosphate

1-Stearoyl-2-[6-[2-[2-(2,6-dichlorophenylamino)phenyl]acetamido]hexanoyl]-*sn*-glycero-3-phosphatidylcholine



C46 H74 Cl2 N3 O9 P; Mol wt: 914.9826

ACTION – Diclofenac prodrug useful as an antiinflammatory agent, a representative compound from a series of phospholipid derivatives of nonsteroidal antiinflammatory drugs (NSAIDs) that act as prodrugs of NSAIDs; these compounds are designed to be cleaved by phospholipases such as PLA₂ that are specifically elevated at disease sites, thus resulting in accumulation of the active drug at the site of the disease while only low levels of prodrug cleavage occur in healthy tissue. Compound exhibited at 30 mg/kg p.o. comparable antiinflammatory activity to diclofenac at 10 mg/kg p.o. in the carrageenan-induced paw edema test in rats, and it also showed significant neuroprotective activity in a global forebrain ischemia model in gerbils at 30 mg/kg p.o., while diclofenac at 10 mg/kg p.o. exhibited weak activity. In addition, it exhibited greatly reduced subchronic toxicity in rats at 30 mg/kg/day p.o. x 14 days compared to diclofenac at 10 mg/kg p.o., as measured by body weight changes, and was found to be clearly less ulcerogenic in these animals. Another exemplified prodrug is:



290678: C44 H70 Cl2 N3 O9 P

SOURCE – D-Pharm.

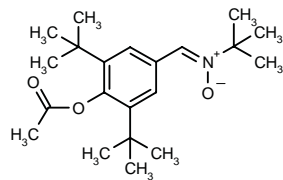
REFERENCES

1. Kozak, A. and Shapiro, I. (D-Pharm Ltd.) *Phospholipid derivs. of non-steroidal anti-inflammatory drugs*. WO 0031083.

290729

N-(4-Acetoxy-3,5-di-*tert*-butylbenzylidene)-*N*-*tert*-butylamine *N*-oxide

C-(4-Acetoxy-3,5-di-*tert*-butylphenyl)-*N*-*tert*-butylnitrone



C21 H33 N O3; Mol wt: 347.4957

ACTION – Antiinflammatory agent, a representative compound from a series of 3,4,5-trisubstituted aryl nitrones that act via inhibition of the induction of cyclooxygenase type 2 (COX-2) rather than by direct inhibition of the enzymes COX-1 or COX-2. Potentially useful for the treatment of inflam-mation-related conditions including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, systemic lupus erythematosus, inflammatory bowel disease, septic shock, adult respiratory distress syndrome (ARDS), organ rejection and neuro- and cardioinflammatory conditions, as well as for use as an analytical reagent, i.e., as a spin trap for detecting unstable free radicals using electron spin resonance (ESR) spectroscopy and related techniques.

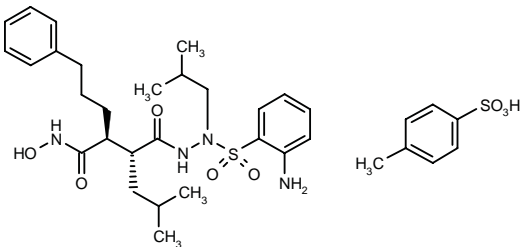
SOURCE – Centaur.

REFERENCES

1. Waterbury, L.D. et al. (Centaur Pharmaceuticals, Inc.) 3,4,5-Trisubstd. aryl nitrone cpds. and pharmaceutical compsns. containing the same. WO 0032567.

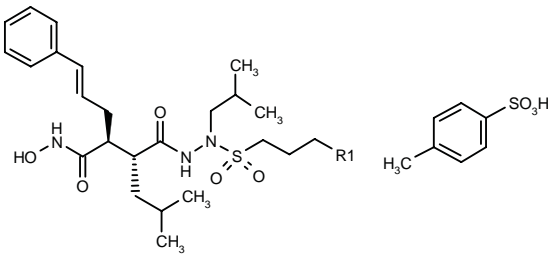
290736

3(*R*)-[2-(2-Aminophenylsulfonyl)-2-isobutylhydrazino-carbonyl]-5-methyl-2(*S*)-(3-phenylpropyl)hexano-hydroxamic acid 4-methylbenzenesulfonate



C27 H40 N4 O5 S . C7 H8 O3 S; Mol wt: 704.9052

ACTION – An inhibitor of TNF- α release (IC₅₀ = 318-866 nM in lipopolysaccharide-stimulated THP1 cells) with potential utility in the treatment of inflammatory and autoimmune diseases, osteoarthritis, respiratory diseases, tumors, cachexia, fever, hemorrhage and sepsis. Other exemplified hydrazine derivatives are:



Compound	R1	Formula
290737	N(Et)2	C ₂₈ H ₄₈ N ₄ O ₅ S.C ₇ H ₈ O ₃ S
290738	NH2	C ₂₄ H ₄₀ N ₄ O ₅ S.C ₇ H ₈ O ₃ S
290739	N(Me)2	C ₂₆ H ₄₄ N ₄ O ₅ S.C ₇ H ₈ O ₃ S
290740	CH2NH2	C ₂₅ H ₄₂ N ₄ O ₅ S.C ₇ H ₈ O ₃ S

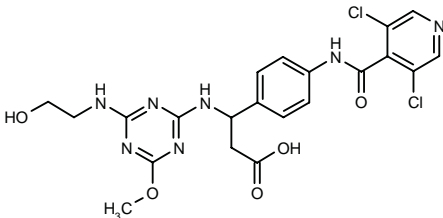
SOURCE – Roche.

REFERENCES

1. Broadhurst, M.J. et al. (F. Hoffmann-La Roche AG) Hydrazine derivs. WO 0032570.

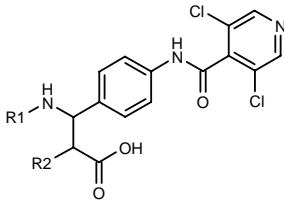
290914

3-[4-(3,5-Dichloropyridin-4-ylcarboxamido)phenyl]-3-[4-(2-hydroxyethylamino)-6-methoxy-1,3,5-triazin-2-ylamino]propionic acid



C21 H21 Cl2 N7 O5; Mol wt: 522.3469

ACTION – Selective inhibitor of $\alpha_4\beta_1$ integrins such as $\alpha_4\beta_1$ and/or $\alpha_4\beta_7$, with potential in the treatment and prevention of immune and inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, allograft rejection, diabetes, psoriasis, dermatitis, asthma and inflammatory bowel disease. Other specifically claimed compounds from this series of β -alanine derivatives are:



Compound	R1	R2	Formula
290915	3,5-(Cl)2-4-Pyr-CO	H	C ₂₁ H ₁₄ Cl ₄ N ₄ O ₄
290916	2,6-(MeO)2-PhCO	H	C ₂₄ H ₂₁ Cl ₂ N ₃ O ₆
290917	3-Ac-4(S)-thiazolidinyl-CO	H	C ₂₁ H ₂₀ Cl ₂ N ₄ O ₅ S
290918	N-[3,5-(Cl)2-PhSO2]-L-Pro-	H	C ₂₆ H ₂₂ Cl ₄ N ₄ O ₆ S
290919	N-[3,5-(Cl)2-PhSO2]-L-Pro-	OH	C ₂₆ H ₂₂ Cl ₄ N ₄ O ₇ S
290920	2-[2,5-(MeO)-PhS]-3-Pyr-CO	H	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₆ S

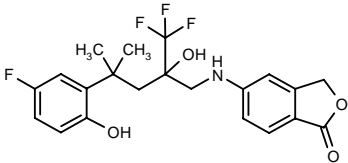
SOURCE – Celltech Group.

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1. Porter, J.R. et al. (Celltech Chiroscience plc) *β-Alanine derivs. as α₄ integrin inhibitors*. WO 0032575.

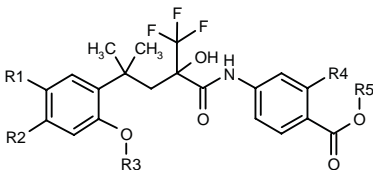
290938

5-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-(trifluoromethyl)pentylamino]-1,3-dihydroisobenzofuran-1-one



C21 H21 F4 N O4; Mol wt: 427.3919

ACTION – Antiinflammatory agent, a representative compound from a series of nonsteroidal derivatives that exhibit high affinity for glucocorticoid receptors (GR) but which, contrary to glucocorticoids, show a clear dissociation between antiinflammatory and metabolic effects, as demonstrated by little or no induction of tyrosine aminotransferase, an enzyme involved in the undesirable metabolic effects of glucocorticoids. Compound exhibited an IC₅₀ value of 2.8 nM for inhibition of [³H]-dexamethasone binding to rat GRs and is reported to inhibit lipopolysaccharide-stimulated IL-8 secretion in human monocytic THP-1 cells by 50-80% at 1 μM and to inhibit croton oil-induced inflammation in mice and rats following topical or systemic application. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4,R5	Formula
290941	F	H	H	-CH2-	C ₂₁ H ₁₉ F ₄ NO ₅
290942	F	H	Me	-C(Me)=N-	C ₂₃ H ₂₂ F ₄ N ₂ O ₅
290943	H	Br	Me	-C(Me)=N-	C ₂₃ H ₂₂ BrF ₃ N ₂ O ₅
290944	F	H	H	-C(Me)=N-	C ₂₂ H ₂₀ F ₄ N ₂ O ₅

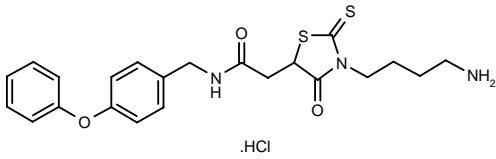
SOURCE – Schering AG.

REFERENCES

1. Lehmann, M. et al. (Schering AG) *Nonsteroidal antiinflammatories*. DE 19856475, WO 0032584.

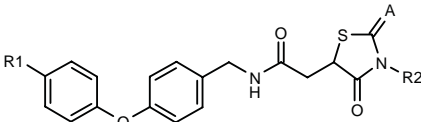
291298

2-[3-(4-Aminobutyl)-4-oxo-2-thioxothiazolidin-5-yl]-N-[4-(phenoxy)benzyl]acetamide hydrochloride



C22 H25 N3 O3 S2 . HCl; Mol wt: 480.0504

ACTION – Matrix metalloproteinase MMP-13 (collagenase 3) inhibitor (IC₅₀ = 1 nM), expected to be of utility in the treatment of a variety of conditions including osteoarthritis, rheumatoid arthritis, osteoporosis, cancer, periodontal disease, corneal ulcer, Paget's disease, nephritis, arteriosclerosis, pulmonary emphysema, autoimmune disease, etc. Other exemplified thiazolidine derivatives are:



Compound	R1	R2	A	Formula
291299	Me	i-Bu	S	C ₂₃ H ₂₆ N ₂ O ₃ S ₂
291300	H	H	O	C ₁₈ H ₁₆ N ₂ O ₄ S
291301	H	(CH ₂) ₃ NH ₂	O	C ₂₁ H ₂₃ N ₃ O ₄ S
291302	H	2-oxo-1-pyrrolidinyl-(CH ₂) ₃	O	C ₂₅ H ₂₇ N ₃ O ₅ S

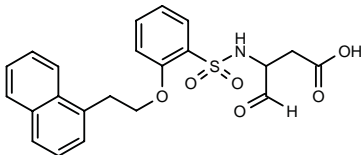
SOURCE – Takeda.

REFERENCES

1. Kawamura, N. et al. (Takeda Chemical Industries, Ltd.) *Novel thiazolidine derivs., their preparation method and use*. JP 2000143650.

291312

3-[2-[2-(1-Naphthyl)ethoxy]phenylsulfonamido]-4-oxo-butyric acid



C22 H21 N O6 S; Mol wt: 427.4749

ACTION – Agent for the treatment of stroke, reperfusion injury, Alzheimer's disease, inflammatory disorders such as arthritis and inflammatory bowel disease, septic shock and shigellosis, an inhibitor of IL-1β-converting enzyme (ICE or caspase 1; K_i = 0.062 μM; IC₅₀ = 0.40 μM) and of other cysteine proteases from the ICE family such as Ich-2 (caspase 4; IC₅₀ = 2.3 μM). Compound was also shown to inhibit IL-1β production in human peripheral blood mononuclear cells (PBMCs; IC₅₀ = 8.0 μM), while exhibiting no cytotoxicity (TC₅₀ > 100 μM). A representative compound from a series of sulfonamide-substituted aspartic acid derivatives.

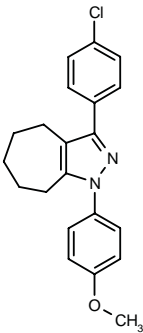
SOURCE – Pfizer.

REFERENCES

1. Allen, H.J. et al. (Warner-Lambert Co.) *Sulfonamide substd. aspartic acid interleukin-1β converting enzyme inhibitors*. US 6083981, WO 9816504.

291313

3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole



C21 H21 Cl N2 O; Mol wt: 352.8629

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2), as demonstrated *in vitro* by IC₅₀ values of 1.56 and 0.38 μM against COX-2 in human umbilical cord endothelial ECV-304 cells and COS-7 cells transfected with human COX-2, respectively, compared to IC₅₀ values of > 10 and 5.3 μM for inhibition of COX-1 in human platelets and in COS-7 cells transfected with human COX-1, respectively. An exemplified compound from a series of 1,3- and 2,3-diarylcycloalkano and cycloalkeno pyrazoles.

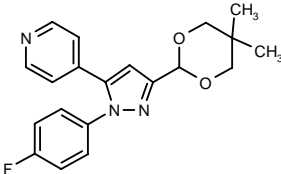
SOURCE – Ortho-McNeil.

REFERENCES

1. Ferro, M. et al. (Ortho-McNeil Pharmaceutical, Inc.) *1,3- And 2,3-diarylcycloalkano and cycloalkeno pyrazoles as selective inhibitors of cyclooxygenase-2 and antiinflammatory agents*. US 6083969.

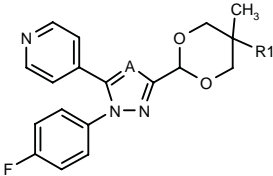
291529

4-[3-(5,5-Dimethyl-1,3-dioxan-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-5-yl]pyridine

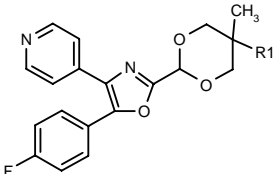


C20 H20 F N3 O2; Mol wt: 353.3950

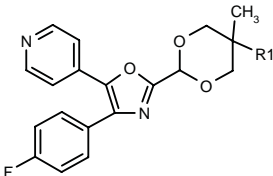
ACTION – TNF-α inhibitor specifically claimed for the treament of asthma and joint inflammation. Other exemplified heteroaryl-cyclic acetals include the following:



Compound	R1	A	Formula
291530	Me	N	C ₁₉ H ₁₉ FN ₄ O ₂
291533	4-morpholinyl-CO	CH	C ₂₄ H ₂₅ FN ₄ O ₄
291534	4-morpholinyl-CO	N	C ₂₃ H ₂₄ FN ₅ O ₄



Compound	R1	Formula
291531	Me	C ₂₀ H ₁₉ FN ₂ O ₃
291535	4-morpholinyl-CO	C ₂₄ H ₂₄ FN ₃ O ₅



Compound	R1	Formula
291532	Me	C ₂₀ H ₁₉ FN ₂ O ₃
291536	4-morpholinyl-CO	C ₂₄ H ₂₄ FN ₃ O ₅

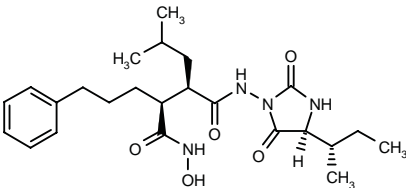
SOURCE – Aventis Pharma.

REFERENCES

1. Collis, A.J. et al. (Rhône-Poulenc Rorer Ltd.) *Heteroaryl-cyclic acetals*. WO 0035911.

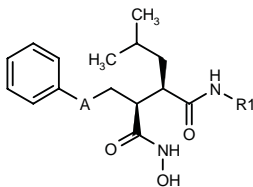
291614

*N*⁴-Hydroxy-2(*R*)-isobutyl-*N*¹-[4(*S*)-[1(*S*)-methylpropyl]-2,5-dioximidazolidin-1-yl]-3(*S*)-(3-phenylpropyl)butane-diamide



C24 H36 N4 O5; Mol wt: 460.5714

ACTION – TNF-α release inhibitor (IC₅₀ = 147 nM for inhibition of lipopolysaccharide-induced TNF-α release from THP-1 cells), potentially useful in the treatment of inflammatory and autoimmune diseases, osteoarthritis, respiratory diseases, tumors, cachexia, cardiovascular disorders, fever, hemorrhage and sepsis. Other exemplified cyclic hydrazine derivatives include the following:



Compound	R1	A	Formula
291615	4(S)-i-Pr-2,5-dioxo-1-imidazolidinyl	-(CH2)2-	C ₂₃ H ₃₄ N ₄ O ₅
291616	4(S)-[(S)-CH(Me)Et]-2,5-dioxo-1-imidazolidinyl	-CH=CH-	C ₂₄ H ₃₄ N ₄ O ₅
291617	2,4-dioxo-1,2,3,4-tetrahydro-1H-thieno[3,2-d]pyrimidin-3-yl	-(CH2)2-	C ₂₃ H ₂₈ N ₄ O ₅ S
291618	2,4-dioxo-1,2,3,4-tetrahydro-thieno[3,4-d]pyrimidin-3-yl	-(CH2)2-	C ₂₃ H ₂₈ N ₄ O ₅ S

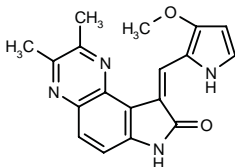
SOURCE – Roche.

REFERENCES

1. Broadhurst, M.J. et al. (F. Hoffmann-La Roche AG) *Cyclic hydrazine derivs. as TNF-α inhibitors*. WO 0035885.

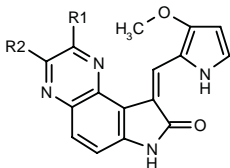
291646

2,3-Dimethyl-9-[(Z)-(3-methoxy-1H-pyrrol-2-yl)methylene]-8,9-dihydro-7H-pyrrolo[3,2-f]quinoxalin-8-one



C18 H16 N4 O2; Mol wt: 320.3504

ACTION – JNK protein kinase inhibitor for the treatment of inflammatory and neurodegenerative diseases, particularly rheumatoid arthritis. The compound was active in an SAPK (the rat homologue of JNK) flashplate assay, exhibiting at least 50% inhibition at < 0.1 μM. Other specifically claimed 4,5-pyrazinoindoles are:



Compound	R1	R2	Formula
291647	Me	Bu	C ₂₁ H ₂₂ N ₄ O ₂
291648	Bu	Me	C ₂₁ H ₂₂ N ₄ O ₂
291649	Me	Ph	C ₂₃ H ₁₈ N ₄ O ₂
291651	Ph	Me	C ₂₃ H ₁₈ N ₄ O ₂
291652	2-furyl	2-furyl	C ₂₄ H ₁₆ N ₄ O ₄
291653	-(CH2)4-		C ₂₀ H ₁₈ N ₄ O ₂

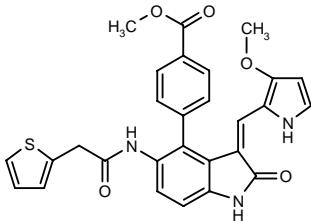
SOURCE – Roche.

REFERENCES

1. Luk, K.-C. and Michoud, C. (F. Hoffmann-La Roche AG) *4,5-Pyrazinoxindoles as protein kinase inhibitors*. WO 0035921.

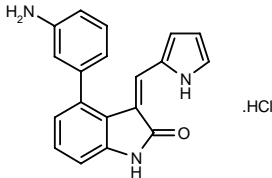
291654

4-[3-[(Z)-(3-Methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-5-[2-(2-thienyl)acetamido]-2,3-dihydro-1H-indol-4-yl]-benzoic acid methyl ester



C28 H23 N3 O5 S; Mol wt: 513.5717

ACTION – JNK protein kinase inhibitor for the treatment of inflammatory and neurodegenerative diseases, particularly rheumatoid arthritis. The compound was active in an SAPK (the rat homologue of JNK) flashplate assay (IC₅₀ < 0.15 μM) and inhibited lipopolysaccharide-induced release of the JNK pathway-related inflammatory mediators TNF (IC₅₀ = 1.35 μM) and IL-6 (IC₅₀ = 7.80 μM) in U937 cells. Another representative compound from this series of 4-aryloxyindoles is:



291655: C19 H15 N3 O . HCl

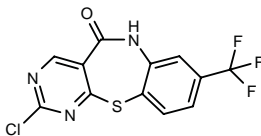
SOURCE – Roche.

REFERENCES

1. Corbett, W.L. et al. (F. Hoffmann-La Roche AG) *4-Aryloxindoles as inhibitors of JNK protein kinases*. WO 0035909.

292098

2-Chloro-8-(trifluoromethyl)pyrimido[4,5-b][1,5]benzothiazepin-5(6H)-one



C12 H5 Cl F3 N3 O S; Mol wt: 331.7045

ACTION – Potent inhibitor of activator protein-1 (AP-1)- and nuclear factor κ-B (NF-κB)-mediated transcriptional activity (IC₅₀ = 0.1 and 0.2 μM, respectively, in Jurkat T-cells transfected with AP-1 and NF-κB binding sites), potentially useful for the treatment of diseases mediated by proinflammatory cytokines such as rheumatoid arthritis and asthma.

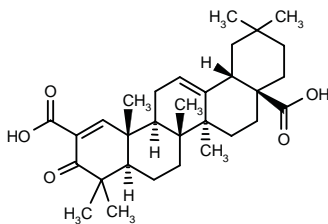
SOURCE – Signal.

REFERENCES

1. Palanki, M.S.S. et al. *Synthesis and structure-activity relationship studies of conformationally restricted analogs of 2-chloro-4-trifluoromethylpyrimidine-5-[N-(3',5'-bis(trifluoromethyl)-phenyl)]carboxamide*. Med Chem Res 2000, 10(1): 19.

292683

3-Oxoolean-1,12(13)-dien-2,28-dioic acid



C31 H44 O5; Mol wt: 496.6836

ACTION – Highly active inhibitor of nitric oxide (NO) production, as demonstrated in mouse macrophages stimulated with interferon gamma ($IC_{50} = 0.07 \mu M$), with potency similar to hydrocortisone ($IC_{50} = 0.01 \mu M$). Unlike hydrocortisone, compound does not act through the glucocorticoid receptor, as its inhibitory effect on NO production could not be blocked by the glucocorticoid antagonist RU-486. Potentially useful as an antiinflammatory and chemopreventive agent.

SOURCE – Dartmouth College, Hanover, NH (US).

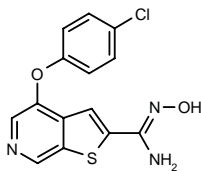
REFERENCES

1. Honda, T. et al. *Novel synthetic oleanane and ursane triterpenoids with various enone functionalities in ring A as inhibitors of nitric oxide production in mouse macrophages*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 151.
2. Honda, T. et al. *Novel synthetic oleanane and ursane triterpenoids with various enone functionalities in ring A as inhibitors of nitric oxide production in mouse macrophages*. J Med Chem 2000, 43(9): 1866.
3. Honda, T. et al. *Novel synthetic oleanane triterpenoids: A series of highly active inhibitors of nitric production in mouse macrophages*. Bioorg Med Chem Lett 1999, 9(24): 3429.

A-293507

292389

4-(4-Chlorophenoxy)-N'-hydroxythieno[2,3-c]pyridine-2-carboxamidide



C14 H10 Cl N3 O2 S; Mol wt: 319.7710

ACTION – Potent and selective inhibitor of TNF- α -induced expression of E-selectin and ICAM-1 ($IC_{50} = 3 \text{ nM}$) on human endothelial cells, potentially useful as an antiinflammatory agent for the treatment of rheumatoid arthritis and inflammatory bowel disease.

SOURCES – Abbott; Lilly.

REFERENCES

1. Lynch, J.K. et al. *Selective inhibition of ICAM-1 and E-selectin expression in human endothelial cells: Replacement of a labile amide at the 2-position of a series of 4-aryloxythieno[2,3-c]pyridines*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 146.

ETORICOXIB*

261533

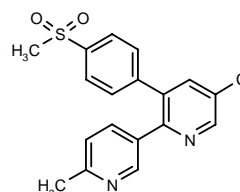
5-Chloro-3-[4-(methylsulfonyl)phenyl]-2-(6-methylpyridin-3-yl)pyridine

5-Chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine

L-791456

MK-0663

MK-663



C18 H15 Cl N2 O2 S; Mol wt: 358.8475

ACTION – Antiinflammatory agent, a potent cyclooxygenase type 2 (COX-2) inhibitor in a cell-based assay ($IC_{50} = 80 \text{ nM}$ in CHO cells stably expressing human COX-2) and human whole blood ($IC_{50} = 1.1 \mu M$) with > 100-fold selectivity over COX-1 ($IC_{50} = 120 \mu M$ for inhibition of PGE_2 production in U937 cells; $IC_{50} = 116 \mu M$ in human whole blood). Compound showed potent antiinflammatory activity in preclinical models of acute and chronic inflammation such as rat carrageenan-induced paw edema and hyperalgesia ($ID_{50} = 0.6$ and $0.3 \text{ mg/kg p.o. b.i.d.}$) and rat adjuvant-induced arthritis ($ID_{50} = 0.7 \text{ mg/kg p.o. b.i.d.}$). No evidence of gastrointestinal toxicity was seen with doses of 100 mg/kg b.i.d. for 10 days. In a phase I clinical study in healthy volunteers dosed with compound at 25, 50, 100 or 150 mg, or placebo, once daily for 9 days, it dose-dependently inhibited lipopolysaccharide-stimulated PGE_2 *ex vivo* and at steady state, an effect persisting for 24 h after dosing. As expected from *in vitro* studies, compound did not show COX-1 inhibition, and no effect was seen on TxB_2 , bleeding time or platelet aggregation. The drug was rapidly absorbed ($t_{max} = 1-2 \text{ h}$) and had a mean elimination half-life of about 15 h. In a triple-blind, randomized, placebo-controlled, multicenter study conducted in 617 patients with knee osteoarthritis, it displayed significantly greater efficacy than placebo and was generally well tolerated. The compound is currently in phase III trials.

SOURCE – Merck & Co.

REFERENCES

1. Block, G.A. and Wold-Olsen, P. (Merck & Co., Inc.) *Method of treating neurodegenerative diseases*. WO 0012093.
2. Boyce, S. et al. (Merck Sharp & Dohme Ltd.) *Use of a COX-2 and a NK-1 receptor antagonist for treating inflammation*. WO 9959635.
3. Corley, E.G. et al. (Merck & Co., Inc.) *Process for synthesizing COX-2 inhibitors*. US 6040319, WO 9955830.
4. Dube, D. et al. (Merck Frosst Canada Inc.) *Substd. pyridines as selective cyclooxygenase-2 inhibitors*. EP 0912518, JP 1999514008, US 5861419, WO 9803484.
5. Nichtberger, S.A. (Merck & Co., Inc.) *Combination therapy and compsns. for acute coronary ischemic syndrome and related conditions*. WO 9945913.
6. Simitchieva, K. et al. (Merck & Co., Inc.) *Method of treating migraines and pharmaceutical compsns*. WO 0025779.

7. Winokur, M. (Merck & Co., Inc.) *Combination therapy for reducing the risks associated with cardio- and cerebrovascular disease*. WO 9920110.

8. Dallob, A. et al. *MK-0663: A highly selective inhibitor of COX-2 in humans*. Ann Rheum Dis 2000, 59(Suppl. 1): Abst POS-279.

9. De Lepeleire, I. et al. *Biochemical activity, safety and pharmacokinetics after multiple doses of MK-0663, a COX-2 specific inhibitor, in healthy volunteers*. 7th World Conf Clin Pharmacol Ther (July 15-20, Florence) 2000, Abst 456.

10. De Lepeleire, I. et al. *MK-0663 (a COX-2 inhibitor) did not affect prednisolone/prednisone plasma levels in healthy volunteers*. 7th World Conf Clin Pharmacol Ther (July 15-20, Florence) 2000, Abst 455.

11. Friesen, R.W. et al. *2-Pyridinyl-3-(4-methylsulfonyl)phenylpyridines: Selective and orally active cyclooxygenase-2 inhibitors*. Bioorg Med Chem Lett 1998, 8(19): 2777.

12. Gottesdiener, K. et al. *MK-663, a specific COX-2 inhibitor for treatment of osteoarthritis (OA) of the knee*. 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abst 444.

13. Gottesdiener, K. et al. *Treatment with MK-663, a specific COX-2 inhibitor, resulted in clinical improvement in osteoarthritis (OA) of the knee that was sustained over three months*. Ann Rheum Dis 2000, 59(Suppl. 1): Abst POS-288.

14. Young, R.N. et al. *Discovery of MK-0663, a highly selective inhibitor of cyclooxygenase-2*. 11th Int Conf Adv Prostaglandin Leukot Res (June 4-8, Florence) 2000, 37.

15. Merck & Co.: *Annual Report 1998*. DailyDrugNews.com (Daily Essentials) 1999, April 13.

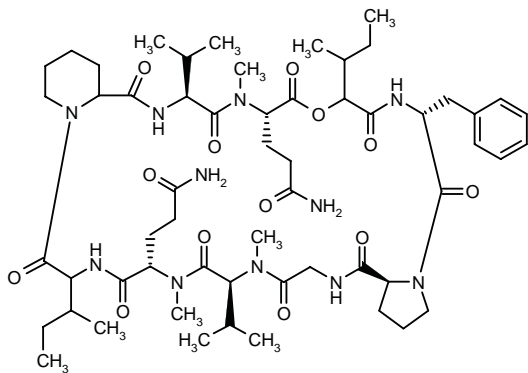
16. *Promising late-stage compounds discussed at Merck & Co. analyst meeting last week*. DailyDrugNews.com (Daily Essentials) 1999, Dec 16.

*Identified compound **261533** Drug Data Rep 1998, 020(05): 0432.

SCH-218157

291924

(6*R*,12*S*,15*S*,27*S*,30*S*,35*aS*)-6-Benzyl-12,27-di(2-carbamoylethyl)-15,30-diisopropyl-13,28,31-trimethyl-9,24-bis(1-methylpropyl)perhydropyrido[1,2-*v*]pyrrolo-[1,2-*g*][1,4,7,10,13,16,19,22,25,28]oxanonaazacyclo-triacontine-5,8,11,14,17,23,26,29,32,35-decaone



C57 H89 N11 O13; Mol wt: 1136.3940

ACTION – Tachykinin NK₂ receptor antagonist (IC₅₀ = 68 nM) isolated from an unidentified fungal fermentation culture broth, with high selectivity over NK₁ receptors (IC₅₀ = 1000 nM). Potentially useful for the treatment of various pathological conditions including inflammation, pain, cancer, anxiety, asthma and vasodilatation.

SOURCE – Schering-Plough.

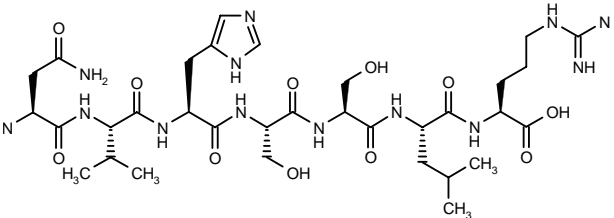
REFERENCES

1. Chu, M. et al. *Structure of Sch 218157, a cyclodepsipeptide with neurokinin activity*. J Antibiot 2000, 53(7): 736.

IMMUNOMODULATING AGENTS

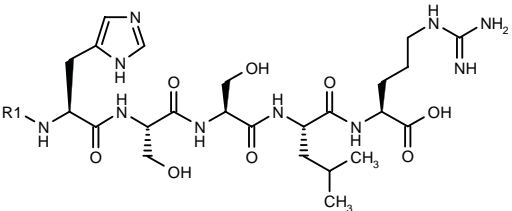
291202

L-Asparaginyl-L-valyl-L-histidyl-L-seryl-L-seryl-L-leucyl-L-arginine



C33 H57 N13 O11; Mol wt: 811.8933

ACTION – Agent that increases active oxygen production in neutrophils, as demonstrated in PMA- or fMLP-stimulated neutrophils obtained from rat abdominal exudates, potentially useful as an immunopotentiating agent and for the prevention of infection. Other exemplified peptides are:



Compound	R1	Formula
291203	H-L-Val-	C ₂₉ H ₅₁ N ₁₁ O ₉
291204	H	C ₂₄ H ₄₂ N ₁₀ O ₈

Some peptides from the invention are reported to inhibit active oxygen production, and may thus be useful for the treatment or prevention of inflammation, sepsis, ulcer and disseminated intravascular coagulation.

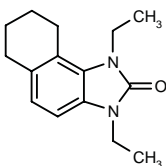
SOURCE – Eisai.

REFERENCES

1. Matsuoka, Y. et al. (Eisai Co., Ltd.) *Peptide with physiological activity*. JP 2000143696.

291350

1,3-Diethyl-2,3,6,7,8,9-hexahydro-1*H*-naphtho[1,2-*d*]-imidazol-2-one



C15 H20 N2 O; Mol wt: 244.3360

7. Winokur, M. (Merck & Co., Inc.) *Combination therapy for reducing the risks associated with cardio- and cerebrovascular disease*. WO 9920110.

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15. Merck & Co.: *Annual Report 1998*. DailyDrugNews.com (Daily Essentials) 1999, April 13.

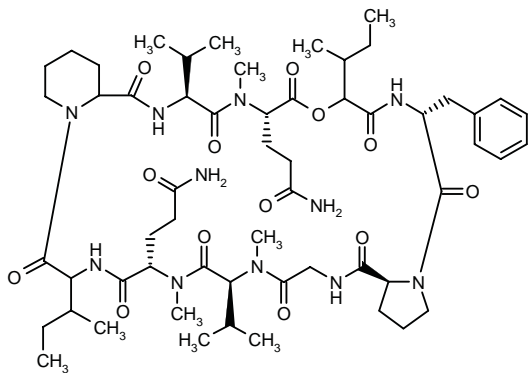
16. *Promising late-stage compounds discussed at Merck & Co. analyst meeting last week*. DailyDrugNews.com (Daily Essentials) 1999, Dec 16.

*Identified compound **261533** Drug Data Rep 1998, 020(05): 0432.

SCH-218157

291924

(6*R*,12*S*,15*S*,27*S*,30*S*,35*aS*)-6-Benzyl-12,27-di(2-carbamoyl-ethyl)-15,30-diisopropyl-13,28,31-trimethyl-9,24-bis(1-methylpropyl)perhydropyrido[1,2-*v*]pyrrolo-[1,2-*g*][1,4,7,10,13,16,19,22,25,28]oxanonaazacyclo-triacontine-5,8,11,14,17,23,26,29,32,35-decaone



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SOURCE – Schering-Plough.

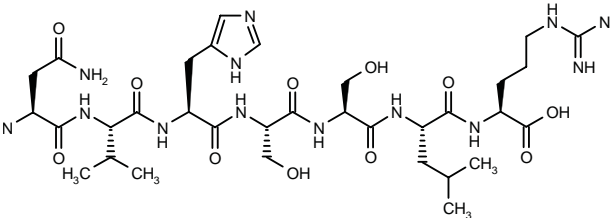
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1. Chu, M. et al. *Structure of Sch 218157, a cyclodepsipeptide with neurokinin activity*. J Antibiot 2000, 53(7): 736.

IMMUNOMODULATING AGENTS

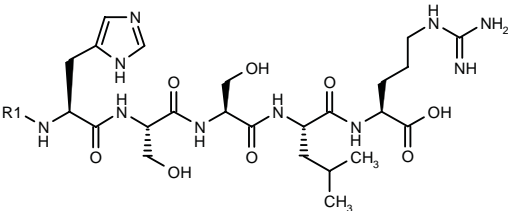
291202

L-Asparaginyl-L-valyl-L-histidyl-L-seryl-L-seryl-L-leucyl-L-arginine



C33 H57 N13 O11; Mol wt: 811.8933

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Compound	R1	Formula
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291204	H	C ₂₄ H ₄₂ N ₁₀ O ₈

Some peptides from the invention are reported to inhibit active oxygen production, and may thus be useful for the treatment or prevention of inflammation, sepsis, ulcer and disseminated intravascular coagulation.

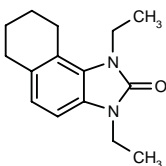
SOURCE – Eisai.

REFERENCES

1. Matsuoka, Y. et al. (Eisai Co., Ltd.) *Peptide with physiological activity*. JP 2000143696.

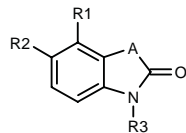
291350

1,3-Diethyl-2,3,6,7,8,9-hexahydro-1*H*-naphtho[1,2-*d*]-imidazol-2-one

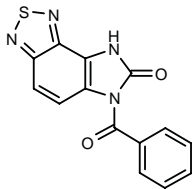


C15 H20 N2 O; Mol wt: 244.3360

ACTION – Potassium channel modulator, particularly active at calcium-activated SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels, for the treatment of diseases or conditions associated with these channels and preferably for reducing or inhibiting undesired immunoregulatory actions. Other exemplified compounds from this series of benzimidazolone, benzoxazolone and benzothiazolone derivatives include the following:



Compound	R1	R2	R3	A	Formula
291351	-(CH2)4-		Et	NH	C ₁₃ H ₁₆ N ₂ O
291352	-CH=CHCH=CH-		Et	O	C ₁₃ H ₁₁ NO ₂
291353	-CH=CHCH=CH-		Et	NH	C ₁₃ H ₁₂ N ₂ O
291355	-N=CHCH=CH-		Et	NH	C ₁₂ H ₁₁ N ₃ O
291356	Cl	Cl	Et	NH	C ₉ H ₆ Cl ₂ N ₂ O
291357	Cl	Cl	Et	N(Et)	C ₁₁ H ₁₂ Cl ₂ N ₂ O
291358	H	Cl	H	O	C ₇ H ₄ ClNO ₂
291359	H	Cl	Et	O	C ₉ H ₆ ClNO ₂



291354: C14 H8 N4 O2 S

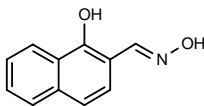
SOURCE – NeuroSearch.

REFERENCES

1. Teuber, L. et al. (NeuroSearch A/S) *New benzimidazolone-, benzoxazolone-, or benzothiazolone derivs. as ion channel modulating agents.* WO 0034248.

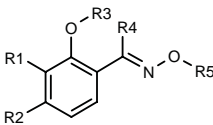
291360

1-Hydroxynaphthalene-2-carbaldehyde oxime



C11 H9 N O2; Mol wt: 187.1971

ACTION – Potassium channel modulator, particularly active at calcium-activated SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels, potentially useful for the treatment of diseases or conditions associated with these channels and preferably for reducing or inhibiting undesired immunoregulatory actions. Other exemplified oximes include the following:



Compound	R1	R2	R3	R4	R5	Formula
291361	-CH=CHCH=CH-		H	Me	H	C ₁₂ H ₁₁ NO ₂
291362	Me	Me	H	H	H	C ₉ H ₁₁ NO ₂
291363	Cl	Cl	H	H	H	C ₇ H ₅ Cl ₂ NO ₂
291364	Cl	Cl	H	H	COPh	C ₁₄ H ₉ Cl ₂ NO ₃
291365	Cl	Cl	H	H	Me	C ₈ H ₇ Cl ₂ NO ₂
291366	-CH=CHCH=CH-		Me	Me	H	C ₁₃ H ₁₃ NO ₂
291367	-CH=CHCH=CH-		Me	Me	Et	C ₁₅ H ₁₇ NO ₂
291368	-CH=CHCH=CH-		Et	Me	H	C ₁₄ H ₁₅ NO ₂
291369	Me	Me	H	Me	H	C ₁₀ H ₁₃ NO ₂
291370	Me	Me	Me	Me	H	C ₁₁ H ₁₅ NO ₂
291371	OMe	OMe	H	Me	H	C ₁₀ H ₁₃ NO ₄
291372	OMe	OMe	Me	Me	H	C ₁₁ H ₁₅ NO ₄
291373	-(CH2)4-		H	Me	H	C ₁₂ H ₁₅ NO ₂
291374	-(CH2)4-		Me	Me	H	C ₁₃ H ₁₇ NO ₂
291375	-(CH2)4-		H	H	H	C ₁₁ H ₁₃ NO ₂

SOURCE – NeuroSearch.

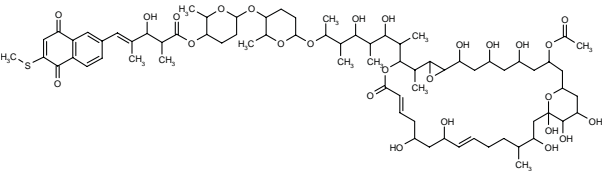
REFERENCES

1. Jensen, B.S. et al. (NeuroSearch A/S) *Ion channel modulating agents.* WO 0034228.

A-77951

290900

3-Hydroxy-2,4-dimethyl-5-[6-(methylsulfonyl)-5,8-dioxo-5,8-dihydronaphthalen-2-yl]-4(E)-pentenoic acid 6-[6-[6-(3-acetoxy-5,7,9,20,22,28,30,31,32-nonahydroxy-13,27-dimethyl-16-oxo-11,15,34-trioxatricyclo[28.3.1.0^{10,12}]-tetratriaconta-17,23-dien-14-yl)-3,5-dihydroxy-1,2,4-trimethylheptyloxy]-2-methyltetrahydro-2H-pyran-3-yloxy]-2-methyltetrahydro-2H-pyran-3-yl ester



C75 H114 O26 S; Mol wt: 1463.7660

ACTION – Immunosuppressive and antifungal macrolide isolated from a culture of *Streptomyces* sp. SANK-66797 (FERM BP-6235). *In vitro*, compound inhibited the mixed lymphocyte reaction (MLR) in human peripheral blood lymphocytes (67.7% inhibition at 0.00001 µg/ml), while it exhibited no cytotoxicity against human-derived U937 cells at concentrations up to 0.1 µg/ml.

SOURCE – Sankyo.

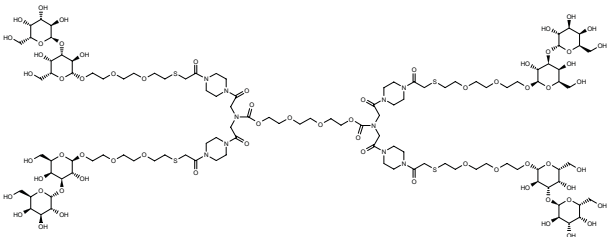
REFERENCES

1. Serizawa, N. et al. (Sankyo Co., Ltd.) *Macrolide cpds. and method for evaluating immunosuppressants.* JP 2000226391, WO 0032604.

LJP-712

291061

4-Cascade:2,13-dioxo-3,6,9,12-tetraoxa-1,14-diazatetra-decane[4-1,1,14,14]:(1-oxoethyl):(piperazine-4,1-diyl):(1,4,7-trioxa-12-oxo-10-thiadodecyl):3-O-(α-D-galactopyranosyl)-β-D-galactopyranose



C112 H192 N10 O66 S4; Mol wt: 2863.0170

ACTION – A representative compound from a series of novel conjugates comprising galactose α-1,3-galactosyl (αGal) epitopes that exhibit significantly increased ability to bind to anti-αGal antibodies, potentially useful for reducing levels of circulating anti-αGal antibodies, known to mediate the hyperacute and delayed rejection of xenografts from animals such as pigs, and hence for inhibiting xenotransplantation rejection. In *in vitro* assays, compound was shown to bind anti-αGal Ig and to inhibit the binding of Ig anti-αGal to the αGal-expressing porcine kidney epithelial PK-15 cell line at about 1 mM. When tested *in vivo* in rhesus monkeys at 20 mg/kg/day i.v., compound reduced the anti-αGal IgG response by 24% at day 8 and anti-αGal IgM levels by 12%.

SOURCE – La Jolla Pharmaceutical.

REFERENCES

1. Jack, R.M. et al. (La Jolla Pharmaceutical Co.) *Conjugates comprising galactose α 1,3 galactosyl epitopes and methods of using same*. WO 0034296.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

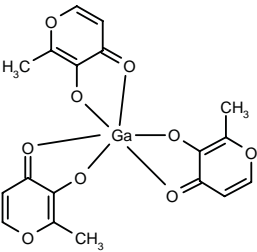
GALLIUM MALTOLATE

291908

Tris[3-(hydroxy-κO)-2-methyl-4H-pyran-4-onato-κO⁴]gallium

Tris(3-hydroxy-2-methyl-4H-pyran-4-onato-O³,O⁴)gallium

GaM



3 C6 H5 Ga O3; Mol wt: 445.0305

ACTION – Orally active gallium compound for the treatment of cancer and other conditions including HIV infection, with moderate water solubility (10.7 mg/ml at 25 °C). Safety and pharmacokinetic studies in healthy volunteers administered single oral doses of 100, 200, 300 and 500 mg showed that it was very well tolerated, oral absorption of gallium into plasma was fairly rapid (0.8-2.0 h), oral gallium bioavailability was approximately 25-57% and urinary gallium excretion was approximately 2% of the dose after 72 h.

SOURCES – GeoMed; Titan.

REFERENCES

1. Bernstein, L.R. (GeoMed, Inc.) *Methods and compsns. to inhibit keratinocyte proliferation*. WO 9804263, WO 9804264.

2. Beatty, E. et al. *Solubility and solvation of pyronato and pyridinato complexes of aluminum, gallium, and indium in alcohol-water mixtures*. Can J Chem 1994, 72(5): 1370.

3. Bernstein, L.R. *Powder X-ray crystallography of gallium 3-hydroxy-4-pyronates*. Powder Diffr 1995, 10(2): 140.

4. Bernstein, L.R. et al. *Chemistry and pharmacokinetics of gallium maltolate, a compound with high oral gallium bioavailability*. Met-Based Drugs 2000, 7(1): 33.

5. Farrar, G. et al. *Tissue distribution of gallium following administration of the gallium-maltol complex in the rat: A model for an aluminium-maltol complex of neurotoxicological interest*. Food Chem Toxicol 1988, 26(6): 523.

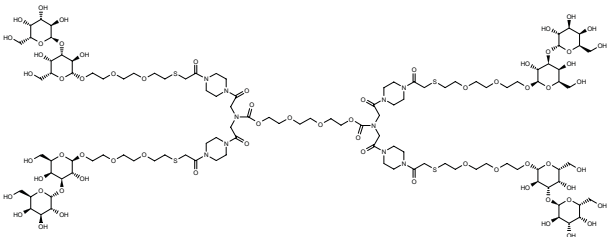
6. Finnegan, M.M. et al. *Neutral water-soluble post-transition-metal chelate complexes of medical interest: Aluminum and gallium tris(3-hydroxy-4-pyronates)*. Inorg Chem 1987, 26(20): 2171.

7. *Titan acquires novel agent for the treatment of cancer and viral disease*. DailyDrugNews.com (Daily Essentials) 2000, July 24.

LJP-712

291061

4-Cascade:2,13-dioxo-3,6,9,12-tetraoxa-1,14-diazatetra-decane[4-1,1,14,14]:(1-oxoethyl):(piperazine-4,1-diyl):(1,4,7-trioxa-12-oxo-10-thiadodecyl):3-*O*-(α -D-galactopyranosyl)- β -D-galactopyranose



C112 H192 N10 O66 S4; Mol wt: 2863.0170

ACTION – A representative compound from a series of novel conjugates comprising galactose α -1,3-galactosyl (α Gal) epitopes that exhibit significantly increased ability to bind to anti- α Gal antibodies, potentially useful for reducing levels of circulating anti- α Gal antibodies, known to mediate the hyperacute and delayed rejection of xenografts from animals such as pigs, and hence for inhibiting xenotransplantation rejection. In *in vitro* assays, compound was shown to bind anti- α Gal Ig and to inhibit the binding of Ig anti- α Gal to the α Gal-expressing porcine kidney epithelial PK-15 cell line at about 1 mM. When tested *in vivo* in rhesus monkeys at 20 mg/kg/day i.v., compound reduced the anti- α Gal IgG response by 24% at day 8 and anti- α Gal IgM levels by 12%.

SOURCE – La Jolla Pharmaceutical.

REFERENCES

1. Jack, R.M. et al. (La Jolla Pharmaceutical Co.) *Conjugates comprising galactose α 1,3 galactosyl epitopes and methods of using same*. WO 0034296.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

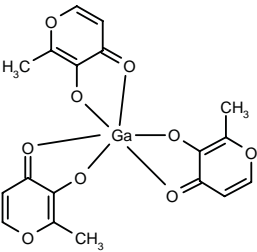
GALLIUM MALTOLATE

291908

Tris[3-(hydroxy- κ O)-2-methyl-4*H*-pyran-4-onato- κ O⁴]gallium

Tris(3-hydroxy-2-methyl-4*H*-pyran-4-onato-*O*³,*O*⁴)gallium

GaM



3 C6 H5 Ga O3; Mol wt: 445.0305

ACTION – Orally active gallium compound for the treatment of cancer and other conditions including HIV infection, with moderate water solubility (10.7 mg/ml at 25 °C). Safety and pharmacokinetic studies in healthy volunteers administered single oral doses of 100, 200, 300 and 500 mg showed that it was very well tolerated, oral absorption of gallium into plasma was fairly rapid (0.8-2.0 h), oral gallium bioavailability was approximately 25-57% and urinary gallium excretion was approximately 2% of the dose after 72 h.

SOURCES – GeoMed; Titan.

REFERENCES

1. Bernstein, L.R. (GeoMed, Inc.) *Methods and compsns. to inhibit keratinocyte proliferation*. WO 9804263, WO 9804264.

2. Beatty, E. et al. *Solubility and solvation of pyronato and pyridinato complexes of aluminum, gallium, and indium in alcohol-water mixtures*. Can J Chem 1994, 72(5): 1370.

3. Bernstein, L.R. *Powder X-ray crystallography of gallium 3-hydroxy-4-pyronates*. Powder Diffr 1995, 10(2): 140.

4. Bernstein, L.R. et al. *Chemistry and pharmacokinetics of gallium maltolate, a compound with high oral gallium bioavailability*. Met-Based Drugs 2000, 7(1): 33.

5. Farrar, G. et al. *Tissue distribution of gallium following administration of the gallium-maltol complex in the rat: A model for an aluminium-maltol complex of neurotoxicological interest*. Food Chem Toxicol 1988, 26(6): 523.

6. Finnegan, M.M. et al. *Neutral water-soluble post-transition-metal chelate complexes of medical interest: Aluminum and gallium tris(3-hydroxy-4-pyronates)*. Inorg Chem 1987, 26(20): 2171.

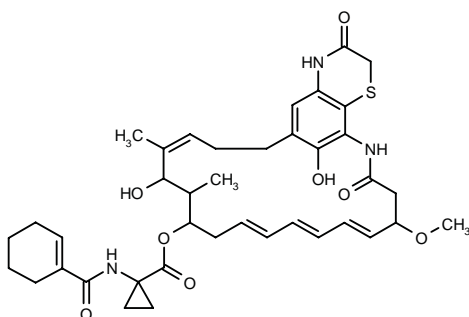
7. Titan acquires novel agent for the treatment of cancer and viral disease. DailyDrugNews.com (Daily Essentials) 2000, July 24.

ANTIBIOTICS AND ALKALOIDS

TMC-135A

291922

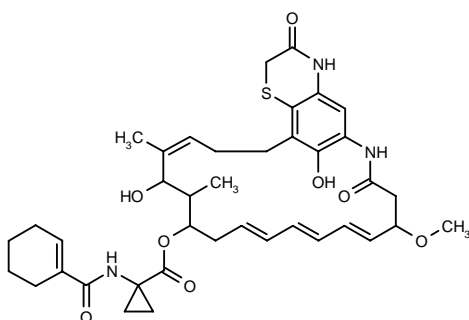
1-(1-Cyclohexen-1-ylcarboxamido)cyclopropane-carboxylic acid 19,26-dihydroxy-9-methoxy-18,20-dimethyl-2,7-dioxo-2,3,6,7,8,9,16,17,18,19,22,23-dodecahydro-1*H*-5,24-metheno[1,4]thiazino[2,3-*c*]azacyclotricosin-17-yl ester



C39 H49 N3 O8 S; Mol wt: 719.8951

Pale yellow powder, *m.p.* 166-8 °C.

ACTION – Antineoplastic antibiotic extracted from the fermentation broth of *Streptomyces* sp. TC 1190, with high cytotoxic activity against a panel of human cancer cells including colon HCT-116 (IC_{50} = 0.07 μ M), breast adenocarcinoma SK-BR-3 (IC_{50} = 0.88 μ M), epithelioid carcinoma HeLa S3, histiocytic lymphoma U-937 (IC_{50} = 0.11 μ M), Raji Burkitt's lymphoma (IC_{50} = 0.05 μ M) and promyelocytic and monocytic leukemia HL-60 and THP1 cells (IC_{50} = 0.05 and 0.06 μ M, respectively). Another triene ansamycin antibiotic produced by this micro-organism is:



TMC-135B [291923]: C39 H49 N3 O8 S

SOURCE – Tanabe Seiyaku.

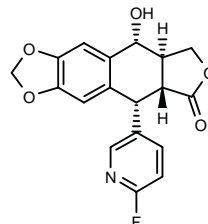
REFERENCES

1. Nishio, M. et al. *TMC-135A and B, new triene-ansamycins, produced by Streptomyces sp.* J Antibiot 2000, 53(7): 724.

ANTIMITOTIC DRUGS

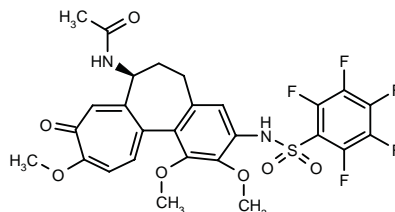
291621

(5*S*,5*aR*8*aR*,9*R*)-5-(6-Fluoropyridin-3-yl)-9-hydroxy-5,6,6*a*,8,8*a*,9-hexahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]-dioxol-6-one

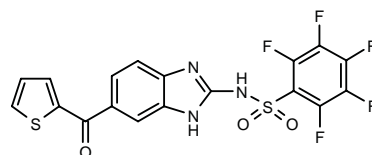


C18 H14 F N O5; Mol wt: 343.3086

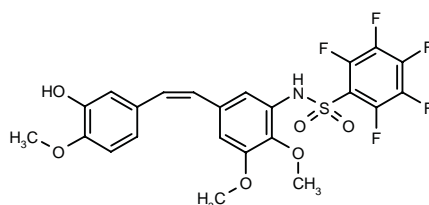
ACTION – Antimitotic agent that acts as a covalent modifier of tubulin and is thus expected to be of use for the treatment of cancer. Other exemplified compounds from this series of derivatives of naturally occurring or known tubulin-binding compounds in which a fluorinated electrophile moiety such as a (poly)fluorobenzene, a fluoropyridine or a fluoronitrophenyl is incorporated into the structure, without interfering with recognition and binding to the tubulin site, include the following:



291620: C27 H23 F5 N2 O7 S



291622: C18 H8 F5 N3 O3 S2



291623: C23 H18 F5 N O6 S

SOURCE – Tularik.

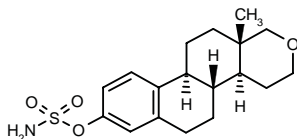
REFERENCES

1. Clark, D. et al. (Tularik Inc.) *Tubulin-binding agents*. WO 0035865.

HORMONAL AGENTS

291619

3-Hydroxy-D-homo-17-oxa-1,3,5(10)-estratriene



C18 H25 N O4 S; Mol wt: 351.4645

ACTION – A representative compound from a series of 3-substituted-D-homo-1,3,5(10)-estratriene derivatives with potent inhibitory activity against estrone sulfatase. Title compound inhibited the activity of this enzyme by 93.7% at 1 nM in human breast cancer MCF-7 cells and by 99.3% at 0.5 mg/kg p.o. in female rats. Potentially useful for the treatment of estrogen-related diseases such as breast, uterine and ovarian cancers, endometriosis, adenomyosis uteri, mastopathy, male gynecomastia, benign prostatic hyperplasia and male infertility due to oligospermia, without causing an increase in liver weight.

SOURCE – Teikoku Hormone.

REFERENCES

1. Koizumi, N. et al. (Teikoku Hormone Manufacturing Co., Ltd.) *3-Substd.-D-homo-1,3,5-(10)-estratriene derivs.* US 6087347, WO 9811124.

CANCER IMMUNOTHERAPY

LMB-2

230373

63-kDa recombinant single-chain immunotoxin composed of the variable domain (Fv) of the anti-interleukin-2 receptor (IL-2R) monoclonal antibody anti-Tac fused to a 38-kDa truncated Pseudomonas exotoxin (PE38)

Anti-Tac(Fv)-PE38

ACTION – Recombinant immunotoxin composed of a single-chain Fv form of the anti-Tac (anti-CD25) monoclonal antibody to the primate IL-2 receptor α subunit (IL-2R α) fused to a 38-kDa fragment of *Pseudomonas* endotoxin. Compound exhibited strong cytotoxic activity against CD25+ cells, produced complete regression of CD25+ tumors in mice and was well tolerated in animals, and is currently being evaluated in phase I trials in patients with CD25+ hematological malignancies. Site-specific pegylation of the immunotoxin is reported to improve antitumor activity and reduce animal toxicity and immunogenicity.

SOURCE – National Institutes of Health, Bethesda, MD (US).

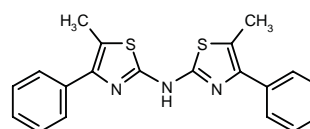
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1. Kreitman, R.J. and Pastan, I. *Biodistribution of recombinant immunotoxin anti-Tac(Fv)-PE38 in mice.* Proc Amer Assoc Cancer Res 1996, 37: Abst 3025.
2. Kreitman, R.J. et al. *Antitumor activity of recombinant immunotoxin anti-Tac(Fv)-PE38 (LMB-2) in patients with hematologic malignancies.* Proc Amer Assoc Cancer Res 1999, 40: Abst 2811.
3. Kreitman, R.J. et al. *Complete remissions in hairy cell leukemia, induced by recombinant immunotoxins targeting CD22, are associated with increases in cytotoxic T-cells.* Proc Am Soc Clin Oncol 2000, 19: Abst 1792.
4. Kreitman, R.J. et al. *New biotherapeutic agents effective in chemotherapy - Refractory hairy cell leukemia: Recombinant immunotoxins targeting CD25 or CD22.* Proc Amer Assoc Cancer Res 2000, 41: Abst 3464.
5. Kreitman, R.J. et al. *Phase I clinical trial of recombinant immunotoxin anti-Tac(Fv)-PE38 (LMB-2) in patients with hematologic malignancies.* Blood 1997, 10(Suppl. 1, Part 1): Abst 2282.
6. Kreitman, R.J. et al. *Phase I clinical trial with recombinant immunotoxin anti-Tac(Fv)-PE38 (LMB-2) in patients with hematologic malignancies.* Proc Amer Assoc Cancer Res 1997, 38: Abst 4089.
7. Kreitman, R.J. et al. *Phase I trial of recombinant immunotoxin anti-Tac(Fv)-PE38 (LMB-2) in patients with hematologic malignancies.* Blood 1998, 92(10, Suppl. 1, Part 1): Abst 1708.
8. Kreitman, R.J. et al. *Phase I trial of recombinant immunotoxin anti-Tac(Fv)PE38 (LMB-2) in patients with hematologic malignancies.* J Clin Oncol 2000, 18(8): 1622.
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10. Kreitman, R.J. et al. *Recombinant immunotoxins containing anti-Tac(Fv) and derivatives of Pseudomonas exotoxin produce complete regression in mice of an interleukin-2 receptor-expressing human carcinoma.* Blood 1994, 83(2): 426.
11. Kreitman, R.J. et al. *Responses in patients with hairy cell leukemia to recombinant immunotoxin Anti-Tac(Fv)-PE38 (LMB-2).* Blood 1998, 92(10, Suppl. 1, Part 1): Abst 1708.5.
12. Onda, M. et al. *Lowering the isoelectric point of the Fv portion of immunotoxin anti-Tac(Fv)-PE38 reduces nonspecific animal toxicity.* FASEB J 2000, 14(8): Abst 264.
13. Onda, M. et al. *Reduction of the nonspecific animal toxicity of anti-Tac (Fv)-PE38 by mutations in the framework regions of the Fv which lower this isoelectric point.* J Immunol 1999, 163(11): 6072.
14. Onda, M. et al. *Reduction of the nonspecific toxicity of immunotoxin anti-Tac(Fv)-PE38 (LMB-2) by mutations in the Fv which lower the isoelectric point.* 41st Annu Meet Am Soc Hematol (Dec 3-7, New Orleans) 1999, Abst 1246.
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18. Tsutsumi, Y. et al. *Site-specific chemical modification with polyethylene glycol of recombinant immunotoxin anti-Tac(Fv)-PE38 (LMB-2) improves antitumor activity and reduces animal toxicity and immunogenicity.* Proc Natl Acad Sci USA 2000, 97(15): 8548.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

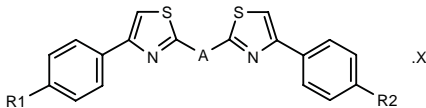
291144

N,N-Bis(5-methyl-4-phenylthiazol-2-yl)amine



C20 H17 N3 S2; Mol wt: 363.5073

ACTION – Antineoplastic agent that acts by inhibiting membrane-associated tyrosine and threonine (myt1) kinase. Other specifically claimed compounds are:



Compound	R1=R2	A	X	Formula
291145	OMe	-NH-1,4-Ph-NH-		C ₂₆ H ₂₂ N ₄ O ₂ S ₂
291147	Ph	-NH-		C ₃₀ H ₂₁ N ₃ S ₂
291148	Ph	-NH-1,4-Ph-NH-	HBr	C ₃₆ H ₂₆ N ₄ S ₂ ·HBr

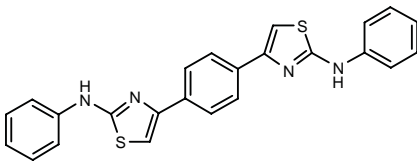
SOURCE – SmithKline Beecham.

REFERENCES

1. Lago, M.A. (SmithKline Beecham Corp.) *Myt1 kinase inhibitors*. WO 0033842.

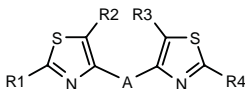
291149

1,4-Bis[2-(Phenylamino)thiazol-4-yl]benzene



C24 H18 N4 S2; Mol wt: 426.5662

ACTION – Inhibitor of membrane-associated tyrosine and threonine (myt1) kinase that is therefore expected to be of use for the treatment of cancer. Other specifically claimed compounds include the following:



Compound	R1=R4	R2	R3	A	Formula
291150	Ph	H	Br	-1,4-Ph-	C ₂₄ H ₁₅ BrN ₂ S ₂
291151	NHPh	Br	Br	-1,4-Ph-	C ₂₄ H ₁₆ Br ₂ N ₄ S ₂
291152	3-Pyr-NH	H	H	-1,4-Ph-	C ₂₂ H ₁₆ N ₆ S ₂
291154	3-Pyr-NH	H	Br	-1,4-Ph-	C ₂₂ H ₁₅ BrN ₆ S ₂
291158	2-Pyr-NH	H	H	-1,4-Ph-	C ₂₂ H ₁₆ N ₆ S ₂
291159	3-Pyr-NH	H	H	1,3-Ph	C ₂₂ H ₁₆ N ₆ S ₂
291160	2-Pyr-NH	H	H	bond	C ₁₆ H ₁₂ N ₆ S ₂

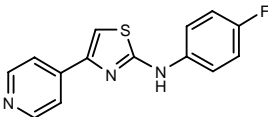
SOURCE – SmithKline Beecham.

REFERENCES

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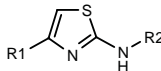
291161

N-(4-Fluorophenyl)-*N*-[4-(4-pyridinyl)thiazol-2-yl]amine



C14 H10 F N3 S; Mol wt: 271.3180

ACTION – Myt1 (membrane-associated tyrosine and threonine) kinase inhibitor, potentially useful for the treatment of cancer. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
291162	4-F-Ph	4-F-Ph	C ₁₅ H ₁₀ F ₂ N ₂ S
291163	3-[3,4-(Cl)2-Ph]-5-isoxazolyl	2-Pyr	C ₁₇ H ₁₀ Cl ₂ N ₄ OS
291164	3-[3,4-(Cl)2-Ph]-5-isoxazolyl	3-Pyr	C ₁₇ H ₁₀ Cl ₂ N ₄ OS

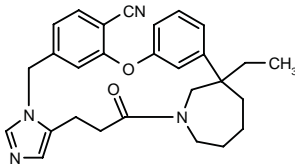
SOURCE – SmithKline Beecham.

REFERENCES

1. Lago, M.A. (SmithKline Beecham Corp.) *Myt1 kinase inhibitors*. WO 0033837.

291207

(±)-17-Ethyl-23-oxo-18,19,20,21,23,24-hexahydro-5*H*,23*H*-17,22-methano-6,10:12,16-dimetheno-imidazo[3,4-*h*][1,11,16]oxadiazacyclodocosane-9-carbonitrile



C28 H30 N4 O2; Mol wt: 454.5710

ACTION – Macrocyclic compound that inhibits protein farnesyltransferase (IC₅₀ = 10 μM or less against human enzyme) and the farnesylation of the oncogene Ras, and is thus expected to be useful in the treatment of diseases associated with cell proliferation such as cancer.

SOURCE – Merck & Co.

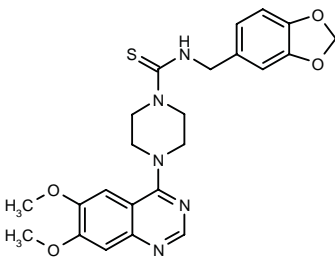
REFERENCES

1. Desolms, S.J. and Shaw, A.W. (Merck & Co., Inc.) *Inhibitors of prenyl-protein transferase*. WO 0034239.

CT-052923*

264407

N-(1,3-Benzodioxol-5-ylmethyl)-4-(6,7-dimethoxyquinazolin-4-yl)piperazine-1-carbothioamide



C23 H25 N5 O4 S; Mol wt: 467.5475

ACTION – Potent and selective platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitor proven to inhibit PDGF receptor and *c-kit* autophosphorylation in cells with respective IC₅₀ values of 40 and 200 nM, whereas it was inactive at up to 30 µM against other receptor tyrosine kinases, serine/threonine kinases or members of the MAPK cascade. Compound specifically inhibited PDGF-induced smooth muscle cell migration and fibroblast proliferation (IC₅₀ = 64 and 280 nM, respectively) and in tissue culture it completely reverted the morphological transformation of NIH/3T3 cells expressing PDGF receptor (PDGF/3T3), but not the oncogenic form of Ras or CSF-1R. In nude mice bearing PDGF/3T3 cells, compound given orally significantly reduced (61%) tumor growth, whereas it was not effective in mice bearing CSF-1R-expressing 3T3 tumors. Considered to have potential particularly as a treatment for human glioblastoma.

SOURCES – COR Therapeutics; Kyowa Hakko.

REFERENCES

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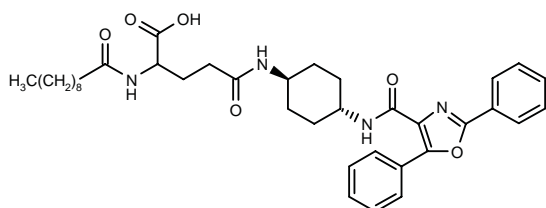
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*Identified compound **264407** Drug Data Rep1998, 020(10): 0854.

FY21-αα09

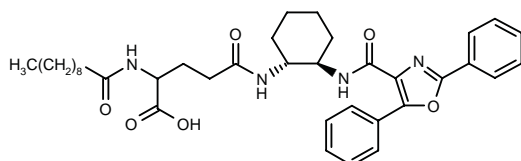
290742

trans-N²-Decanoyl-N⁵-[4-(2,5-diphenyloxazol-4-ylcarbox-amido)cyclohexyl]-DL-glutamine



C37 H48 N4 O6; Mol wt: 644.8082

ACTION – Partial competitive inhibitor of the dual-specificity protein phosphatase (DSPase) Cdc25B (K_i = 1.6 µM), proven to inhibit the growth of human breast cancer MDA-MB-231 and MCF-7 cells (90% inhibition at 100 µM). It partially blocked cell cycle progression at G2/M. Potential lead compound for the development of new antineoplastic agents. Another related compound is:



FY3-αα09 [290689]: C37 H48 N4 O6

SOURCE – University of Pittsburgh, Pittsburgh, PA (US).

REFERENCES

1. Ducruet, A.P. et al. *Identification of new Cdc25 dual specificity phosphatase inhibitors in a targeted small molecule array.* Bioorg Med Chem 2000, 8(6): 1451.

2. Lazo, J.S. and Wipf, P. *Targeted libraries of dual specificity phosphatase inhibitors.* 27th Natl Med Chem Symp (June 13-17, Kansas City) 2000, Abst S-09.

ISIS-20772

291056

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is: CCTTGTTTCCACCATTCC

ACTION – Antisense oligonucleotide targeted to nucleic acids encoding the human G-α-13 protein, a GTP-binding protein or G-protein, and thus expected to be useful in the treatment of hyperproliferative diseases. ISIS-20772 produced a 93% inhibition of G-α-13 mRNA levels at 150 nM in human cells. Other exemplified oligonucleotides are:

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is: CTTTCCCGAGACAGGCA

ISIS-20753 [291057]

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is: ACCCTCATACCTTTGATC

ISIS-20764 [291058]

18-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is: CCGCTGTCTGCCATAAT

ISIS-20776 [291059]

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Cowser, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of G-α-13 expression.* WO 0033889.

ISIS-21028

291064

18-Mer chimeric phosphorothioate oligonucleotide whose sequence is: GGTGGTGGGCACGCGGAC, in which the central ten nucleosides are 2'-deoxynucleosides, the four nucleosides flanking the 5'- and 3'-ends are 2'-O-(2-methoxyethyl)-substituted nucleosides and the cytidine in position 18 is 2'-O-(2-methoxyethyl)-5-methylcytidine

ACTION – Antisense oligonucleotide targeted to nucleic acids encoding the human G-α-11 protein, a member of the family of GTP-binding proteins, substituted or G-proteins. This compound is expected to be useful in the treatment of hyperproliferative diseases such as cancer. ISIS-21028 inhibited G-α-11 mRNA levels by 81% at 150 nM in human cells.

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Cowser, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of G-α-11 expression.* WO 0034301.

ISIS-28949

291680

18-Mer chimeric phosphorothioate oligonucleotide whose sequence is: CTGGCTGACAGAGTGAGG, in which the central ten nucleotides are 2'-deoxynucleotides, the four nucleotides flanking the 5'- and 3'-ends are 2'-O-(2-methoxyethyl)-substituted nucleotides and cytidine in position 1 is 2'-O-(2-methoxyethyl)-5-methylcytidine

ACTION – Antisense oligonucleotide targeted to a nucleic acid encoding the serine/threonine kinase Akt-1 with the ability to modulate the expression of Akt-1, as demonstrated by 90% inhibition of Akt-1 expression in human cells at 150 nM. Akt-1 has been shown to be involved in signaling pathways and to mediate several functions within the cell including apoptosis. This compound is thus expected to be of use for the treatment of hyperproliferative disorders, particularly cancer.

SOURCE – Isis Pharmaceuticals.

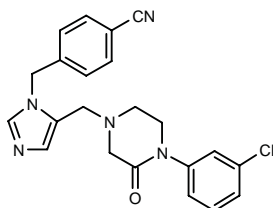
REFERENCES

1. Monia, B.P. and Cowdert, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of Akt-1 expression*. WO 0036149.

L-778123*

243315

4-[5-[4-(3-Chlorophenyl)-3-oxopiperazin-1-ylmethyl]-imidazol-1-ylmethyl]benzonitrile



C22 H20 Cl N5 O; Mol wt: 405.8870

ACTION – Antineoplastic agent, a potent and selective peptidomimetic protein farnesyltransferase inhibitor with synergistic growth-inhibitory activity against human breast cancer cell lines when combined with paclitaxel. Several phase I clinical studies in patients with solid tumors have been completed or are in progress to establish the maximum tolerated dose (MTD) and pharmacokinetic and pharmacodynamic profiles of the compound. All trials have demonstrated that compound is well tolerated at concentrations that produce relevant biological effects in preclinical studies and inhibit protein farnesylation *in vivo*.

SOURCE – Merck & Co.

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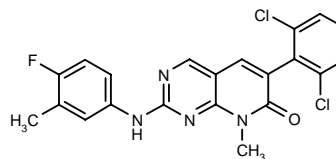
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*Identified compound **243315** (see **242862**) Drug Data Rep 1997, 019(02): 0171.

PD-180970

291664

6-(2,6-Dichlorophenyl)-2-(4-fluoro-3-methylphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one



C21 H15 Cl2 F N4 O; Mol wt: 429.2805

ACTION – Antineoplastic agent, an inhibitor of protein tyrosine kinase proven to inhibit tyrosine phosphorylation of the Bcr-Abl fusion protein p210^{Bcr-Abl} (IC₅₀ = 170 nM), as well as the p210^{Bcr-Abl} substrates Gab2 and CrkL (IC₅₀ = 80 nM) in human chronic myelogenous leukemia K-562 cells. In addition, compound strongly inhibited autophosphorylation of p210^{Bcr-Abl} (IC₅₀ = 5 nM) and the kinase activity of purified recombinant Abl tyrosine kinase (IC₅₀ = 2.2 nM). It induced apoptosis in K-562 cells but did not affect the growth or viability of p210^{Bcr-Abl}-negative human leukemia HL-60 cells.

SOURCE – Pfizer.

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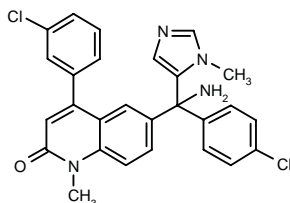
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R-115777*

253457

6-[1-Amino-1-(4-chlorophenyl)-1-(1-methylimidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methylquinolin-2(1H)-one



C27 H22 Cl2 N4 O; Mol wt: 489.4090

ACTION – Antineoplastic agent, a potent and selective inhibitor of protein farnesyltransferase proven to inhibit the farnesylation of lamin B1 ($IC_{50} = 0.8$ nM) and K-*ras* ($IC_{50} = 7.9$ nM) peptide by isolated human enzyme; only 40% inhibition of protein geranylgeranyltransferase I was observed at a concentration of 50 μ M. Compound inhibited the proliferation of H-*ras*-transformed fibroblasts ($IC_{50} = 1.7$ nM) and human colon and pancreatic tumor cell lines bearing K-*ras* mutations ($IC_{50} = 16$ -22 nM against CAPAN-2, HCT-116 and LoVo cells). Compound markedly reduced survival after irradiation of a radioresistant human glioma cell line, with no effect on the survival of radiosensitive SF767 cells. *In vitro* and *in vivo* studies of compound combined with standard chemotherapeutic agents such as paclitaxel or cisplatin demonstrated additive effects without evidence of synergistic or antagonistic interactions. In mice bearing C32 melanoma with wild-type *ras* genes, compound given orally at doses of 25, 50 and 100 mg/kg b.i.d. induced a marked, dose-related increase in tumor cell apoptosis and a statistically significant reduction in angiogenesis at the dose of 50 mg/kg. It was also found to inhibit tumor growth in mice bearing s.c. tumors derived from T24 H-*ras*-transformed NIH3T3 fibroblasts or human tumors with K-*ras* mutations such as human colon LoVo tumors and human pancreatic CAPAN-2 tumors. Phase I and pharmacokinetic studies in patients with advanced cancers demonstrated that compound is bioavailable after oral administration and indicated a recommended dose for phase II studies of 500 mg orally b.i.d. for 5 consecutive days followed by 5 days of rest. It is currently being evaluated in clinical trials for various cancer indications including refractory or relapsed acute myeloid and lymphoid leukemias, breast and bladder cancer, as well as malignant glioma.

SOURCE – Janssen.

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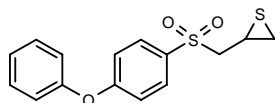
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*Identified compound **253457** Drug Data Rep 1997, 019(10): 0940.

ANGIOGENESIS INHIBITORS

290926

2-(4-Phenoxyphenylsulfonylmethyl)thiirane
4-Phenoxyphenyl 2-thiiranylmethyl sulfone



C15 H14 O3 S2; Mol wt: 306.4046

ACTION – Human gelatinase A and gelatinase B inhibitor ($K_i = 13.9$ and 600 nM, respectively) with high selectivity over other matrix metalloproteinases including stromelysin 1 (MMP-3; $K_i = 15$ μ M), matrilysin (MMP-7; $K_i = 96$ μ M) and interstitial collagenase (MMP-1; $K_i = 206$ μ M). Potentially useful for the treatment of tumor metastases and angiogenesis.

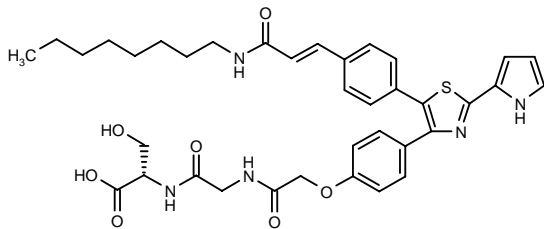
SOURCE – Wayne State University, Detroit, MI (US).

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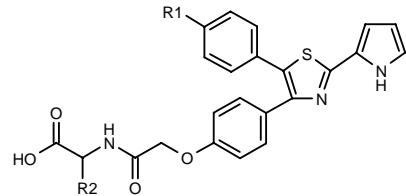
291086

N-[2-[4-[5-[4-(3-Octylamino-3-oxo-1-propenyl)phenyl]-2-(1*H*-pyrrol-2-yl)thiazol-4-yl]phenoxy]acetyl]glycyl-L-serine



C37 H43 N5 O7 S; Mol wt: 701.8407

ACTION – Selective P- and L-selectin inhibitor ($IC_{50} = 0.18$ and 0.16 μ M, respectively, vs. > 500 μ M for E-selectin in human ELISA assays) with potential for the treatment of a broad range of disorders including acute respiratory distress syndrome, angiogenesis, asthma, atherosclerosis, atopic dermatitis, diabetes, multiple sclerosis, myocardial ischemia/reperfusion injury, psoriasis, rheumatoid arthritis and cancer. Compound inhibited HL-60 cell adhesion to P-selectin by 95% at 30 μ M. Other exemplified compounds from this series of substituted thiazoles include the following:



Compound	R1	R2	Formula
291087	CH=CHCONHC6H13	(R)-CH2OH	C ₃₃ H ₃₆ N ₄ O ₆ S
291088	CONHCH2CH(Ph)Et	(S)-CH2OH	C ₃₅ H ₃₄ N ₄ O ₆ S
291089	CH=CHCONHC6H13	CH2CH2CONH2	C ₃₅ H ₃₉ N ₅ O ₆ S

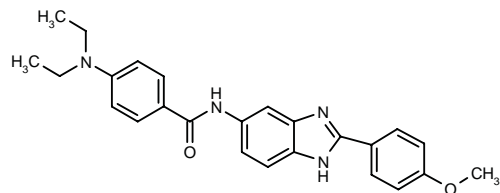
SOURCES – Ontogen; Organon.

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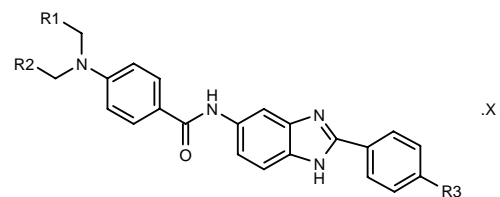
291217

4-(Diethylamino)-*N*-[2-(4-methoxyphenyl)-1*H*-benzimidazol-5-yl]benzamide



C25 H26 N4 O2; Mol wt: 414.5064

ACTION – Neovascularization inhibitor, potentially useful in the treatment of cancer, inflammatory diseases, diabetic retinopathy and atherosclerosis. It inhibited vascular endothelial growth factor (VEGF)-induced proliferation of human umbilical vein endothelial cells (HUVEC) with an IC_{50} of 0.3 nM. Other exemplified benzimidazole derivatives are:



Compound	R1=R2	R3	X	Formula
291218	H	4-N(Me)2-PhCONH		C ₃₁ H ₃₀ N ₆ O ₂
291220	Me	NH2		C ₂₄ H ₂₅ N ₅ O
291221	Me	4-N(Et)2-PhCONH		C ₃₅ H ₃₈ N ₆ O ₂
291223	H	OMe		C ₂₃ H ₂₂ N ₄ O ₂
291225	Me	OMe	2HCl	C ₂₅ H ₂₆ N ₄ O ₂ ·2HCl

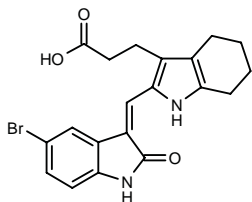
SOURCE – Takeda.

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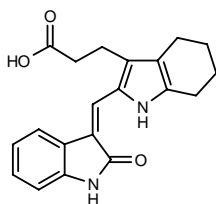
291709^{2,3}

(Z)-3-[2-(5-Bromo-2-oxo-2,3-dihydro-1*H*-indol-3-ylidenemethyl)-4,5,6,7-tetrahydro-1*H*-indol-3-yl]propionic acid



C₂₀ H₁₉ Br N₂ O₃; Mol wt: 415.2851

ACTION – Potent inhibitor of receptor tyrosine kinases associated with vascular endothelial growth factor receptor 2 (VEGF-R2, Flk-1), fibroblast growth factor receptor 1 (FGF-R1) and platelet-derived growth factor receptor β (PDGF-R β), giving respective IC₅₀ values of 0.03, 0.27 and 0.004 μ M; compound was inactive against epidermal growth factor receptor (EGF-R) and poorly active against p60^{c-Src} (IC₅₀ > 100 and 1.27 μ M, respectively). It inhibited VEGF- and FGF-dependent human umbilical vein endothelial cell (HUVEC) proliferation with IC₅₀ values of 0.3 and 100 nM, respectively, but it inhibited PDGF-dependent HUVEC proliferation only at higher concentrations (IC₅₀ = 1.38 μ M). Potentially useful for the treatment of angiogenesis-related diseases including cancer, diabetic retinopathies, atherosclerosis, psoriasis and rheumatoid arthritis. Another indolin-2-one is:



291708¹⁻³: C₂₀ H₂₀ N₂ O₃

SOURCES – Max-Planck Institut für Biochemie, Martinsried (DE); New York University, New York, NY (US); Sugen.

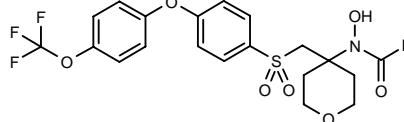
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A-316023

292460

N-Hydroxy-*N*-[4-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonylmethyl]tetrahydro-2*H*-pyran-4-yl]formamide



C₂₀ H₂₀ F₃ N O₇ S; Mol wt: 475.4380

ACTION – Potent gelatinase A and gelatinase B inhibitor (IC₅₀ = 3.6 and 0.63 nM, respectively) with no significant activity against fibroblast collagenase. In monkeys, compound showed good oral bioavailability (33%) and a long half-life (21 h). In mice bearing melanoma B16 cells, compound given twice daily for 14 days induced a dose-dependent reduction in tumor growth (52% at the dose of 30 mg/kg p.o.).

SOURCE – Abbott.

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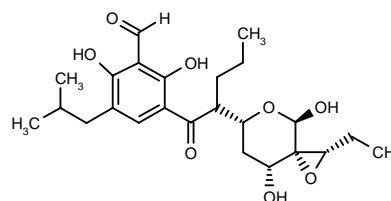
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LUMINACIN D

291273

3-[2-[(2*S*,4*R*,8*R*)-2-Ethyl-4,8-dihydroxy-1,5-dioxaspiro[2.5]oct-6-yl]pentanoyl]-2-hydroxy-5-isobutylbenzaldehyde

VD-1207D



C₂₄ H₃₄ O₈; Mol wt: 450.5246

Pale yellow powder, [α]_D²³ –13.0° (c 0.1 CHCl₃).

ACTION – Angiogenesis inhibitor, a component of a microbial metabolite complex isolated from the fermentation broth of *Streptomyces* sp. Mer-VD1207. Compound inhibited capillary tube formation (IC₅₀ = 0.017 μ g/ml) and the proliferation of human umbilical vein endothelial cells (IC₅₀ = 0.18 μ g/ml) *in vitro*, and it exhibited antiproliferative activity against other cell lines including rat smooth muscle SD6 cells (IC₅₀ = 17.4 μ g/ml), human WI 38 fibroblasts (IC₅₀ = 3.9 μ g/ml), human colon cancer WiDr cells (IC₅₀ = 4.8 μ g/ml), human lung cancer H-520 cells (IC₅₀ = 8.0 μ g/ml) and human breast cancer MDA-MB-434 and MDA-MB-231 cells (IC₅₀ = 8.0 and 5.6 μ g/ml, respectively).

SOURCES – Eisai; Mercian.

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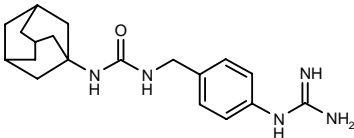
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WX-293T

288711

N-(4-Guanidinobenzyl)-N’-(1-adamantyl)urea



C19 H27 N5 O; Mol wt: 341.4563

ACTION – Urokinase-type plasminogen activator (uPA) inhibitor ($K_i = 2.4 \mu\text{M}$) with high selectivity over other serine proteases such as thrombin ($K_i = 600 \mu\text{M}$), plasmin, factor Xa and tissue plasminogen activator ($K_i > 1000 \mu\text{M}$). Compound is associated with minimal cytotoxicity even at high concentrations and may represent an attractive lead structure for developing potent anti-metastatic drugs.

SOURCES – Friedrich-Schiller-Universität Jena, Jena (DE); Ludwig-Maximilians-Universität München, Munich (DE); Max-Planck-Gesellschaft, München (DE); Wilex.

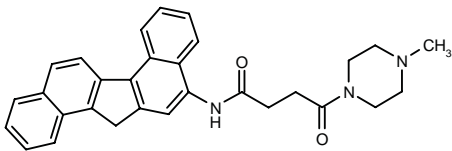
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OTHER ONCOLYTIC DRUGS

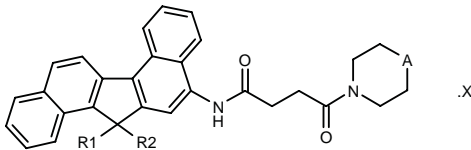
290780

N-(13H-Dibenzo[a,g]fluoren-11-yl)-4-(4-methylpiperazin-1-yl)-4-oxobutyramide



C30 H29 N3 O2; Mol wt: 463.5781

ACTION – Antineoplastic agent with potent *in vitro* cytotoxicity against murine leukemia P388 ($\text{IC}_{50} = 2.0 \mu\text{g/ml}$), human melanoma BRO ($\text{IC}_{50} = 1.8 \mu\text{g/ml}$), human colon adenocarcinoma HT-29 ($\text{IC}_{50} = 1.9 \mu\text{g/ml}$), human breast carcinoma MCF-7 ($\text{IC}_{50} = 3.0 \mu\text{g/ml}$), human ovarian carcinoma OVCAR-3 ($\text{IC}_{50} = 0.19 \mu\text{g/ml}$) and human promyelocytic leukemia HL-60 cells ($\text{IC}_{50} = 1.6 \mu\text{g/ml}$). Other specifically claimed compounds from this series of dibenzofluorene derivatives are:



Compound	R1	R2	A	X	Formula
290783	H	H	N(Me)	HCl	C ₃₀ H ₂₉ N ₃ O ₂ ·HCl
290784	H	OH	N(Me)		C ₃₀ H ₂₉ N ₃ O ₃
290785	-O-		N(Me)		C ₃₀ H ₂₇ N ₃ O ₃
290786	H	OH	CH2		C ₃₀ H ₂₈ N ₂ O ₃

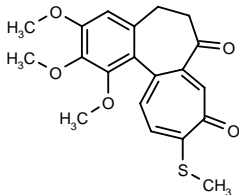
SOURCE – University of Texas System, Austin, TX (US).

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291020

1,2,3-Trimethoxy-10-methylsulfanyl-5,6,7,9-tetrahydro-benzo[a]heptalene-7,9-dione



C20 H20 O5 S; Mol wt: 372.4390

ACTION – Antineoplastic, antiproliferative and anti-inflammatory agent with good oral bioavailability, a representative compound from a series of colchicine derivatives that have the advantage over colchicine of displaying high cytotoxicity both against normal and multidrug-resistant (MDR) cancer cells, as demonstrated *in vitro* against normal and doxorubicin- and vinblastine-resistant breast cancer MCF-7 cells ($\text{IC}_{50} = 6.2$ and 15 nM , respectively, vs. 1.8 and $12,000 \text{ nM}$, respectively, for colchicine and 2.3 and 2400 nM , respectively, for paclitaxel).

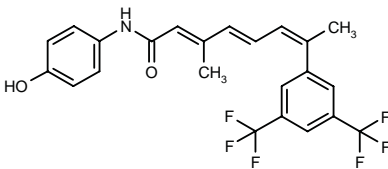
SOURCE – Indena.

REFERENCES

1. Bombardelli, E. (Indena SpA) *Colchicine-skeleton cpds., their use as medicaments and compsns. containing them*. US 6080739, WO 9747577.

291593

7-[3,5-Bis(trifluoromethyl)phenyl]-N-(4-hydroxyphenyl)-3-methyl-2(E),4(E),6(Z)-octatrienamide



C23 H19 F6 N O2; Mol wt: 455.3961

ACTION – A preferred compound from a series of heptatrienoic acid retinamides with apoptotic activity for the treatment of cancer, particularly effective for the therapy of solid tumors, especially non-small cell lung, colorectal and breast carcinomas. The compound caused reduction of cell growth in human breast carcinoma ZR-75-1, MDA-435 and MDA-231 cells, and induced significant apoptosis in MDA-435 and RKO cells after 24 h and in ZR-75-1 cells after 48 h at 1-10 μ M. Both tumor size and tumor number decreased when the compound was administered to rats bearing nitrosomethylurea-induced mammary tumors.

SOURCE – Roche.

REFERENCES

1. Cheung, A.W.-H. et al. (F. Hoffmann-La Roche AG) *7-Aryl-6(Z)heptatrienoic acid retinamides as apoptosis inducing cpds. and their use as anti-cancer agents*. WO 0035856.

ISIS-27067

291681

18-Mer chimeric phosphorothioate oligonucleotide whose sequence is: CTCAGTTGAAGGTTTTGC, in which the central ten nucleotides are 2'-deoxynucleotides, the four nucleotides flanking the 5'- and 3'-ends are 2'-O-(2-methoxyethyl)-substituted nucleotides and cytidines in positions 1, 3 and 18 are 2'-O-(2-methoxyethyl)-5-methylcytidines

ACTION – Antisense oligonucleotide targeted to a nucleic acid encoding human sentrin, a member of the ubiquitin-like family of protein modifiers. The antisense compound modulates the expression of sentrin (81% inhibition of sentrin mRNA levels in human cells at 150 nM) and is thus useful for the treatment of hyperproliferative diseases, in particular cancer, and primary biliary cirrhosis.

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Baker, B.F. and Cowser, L.M. (Isis Pharmaceuticals, Inc.) *Antisense modulation of sentrin expression*. WO 0036148.

JF-05-59

290485

D-Lysyl-L-tyrosyl-L-lysyl-L-tyrosyl-L-lysyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-threoninamide cyclic (S-3.6-S-3.11)-disulfide

C76 H110 N18 O16 S2; Mol wt: 1595.9470

ACTION – A representative compound from a series of hydrophilic somatostatin (SRIF) analogues that may be readily labeled with toxic or nontoxic detectable labels such as iodine atoms, and are useful for specifically targeting somatostatin receptor-bearing cells, in particular neoplastic cells, and may thus be used for the treatment of cancer; in addition, the labeled analogues are useful for tumor localization and detection and, if labeled with a toxic label (e.g., radioactivity), they may be useful for the targeted delivery of toxicity to cancer cells. *In vitro*, compound inhibited rat pituitary growth hormone (GH)

release with an IC₅₀ value of 0.3 nM and was found to potently bind to SRIF receptors, exhibiting K_d values of 4.1, 0.36, 6.4, 515 and 13.4 nM for human sst1, sst2, sst3, sst4 and sst5 receptors, respectively. Another exemplified compound is the iodine-labeled analogue of title compound:

D-Lysyl-L-(3-iodo)tyrosyl-L-lysyl-L-(3-iodo)tyrosyl-L-lysyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-threoninamide cyclic (S-3.6-S-3.11)-disulfide

JF-05-59[I] [290965]: C76 H108 I2 N18 O16 S2

SOURCE – Tulane University, New Orleans, LA (US).

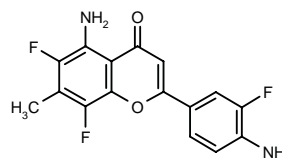
REFERENCES

1. Coy, D.H. et al. (Tulane University) *Hydrophilic somatostatin analogs*. WO 0031122.

NSC-686288*

221218

5-Amino-2-(4-amino-3-fluorophenyl)-6,8-difluoro-7-methyl-4H-1-benzopyran-4-one



C16 H11 F3 N2 O2; Mol wt: 320.2730

ACTION – Antineoplastic agent, an aminoflavone with excellent *in vitro* activity against human renal carcinoma Caki-1 and A-498 cells, human breast carcinoma MCF-7 cells (IC₅₀ = 13 nM) and human lung carcinoma NCI-H226 cells. Studies with human tumor xenografts confirmed the *in vitro* findings; in nude mice, compound induced complete regression of both renal tumor xenografts at doses of 120-200 mg/kg i.p.

SOURCES – Kyowa Hakko; National Cancer Institute, Bethesda, MD (US).

REFERENCES

1. Akama, T. et al. (Kyowa Hakko Kogyo Co., Ltd.) *5-Aminoflavone derivs., their preparation and their use as antibacterial, anti-estrogenic and/or antitumor agent*. EP 0638566, JP 1995109268.
2. Akama, T. et al. *Structure-activity relationships of the 7-substituents of 5,4'-diamino-6,8,3'-trifluoroflavone, a potent antitumor agent*. J Med Chem 1998, 41(12): 2056.
3. Alley, M.C. et al. *Pharmacologic evaluations of a novel amino-substituted flavone (NSC 686288) exhibiting unique in vitro and in vivo anticancer activities*. Proc Amer Assoc Cancer Res 1999, 40: Abst 790.
4. Brown, A.P. et al. *Intravenous plasma elimination kinetics and toxicity of an aminoflavone in the dog*. Proc Amer Assoc Cancer Res 1999, 40: Abst 2579.
5. Dykes, D.J. et al. *Marked activity of an aminoflavone (NSC 686288) against human renal tumors in athymic nude mice*. Proc Amer Assoc Cancer Res 1999, 40: Abst 788.
6. Kuffel, M.J. et al. *Tumor cell- and tissue-selective cytochrome P450 oxidation of aminoflavone analog NSC 686088 (AF)*. Proc Amer Assoc Cancer Res 2000, 41: Abst 2347.
7. Phillips, L.R. et al. *Identification of the principal circulating metabolite of a synthetic 5,4'-diaminoflavone (NSC 686288), an antitumor agent, in the rat*. J Chromatogr B - Biomed Sci Appl 2000, 741(2): 205.

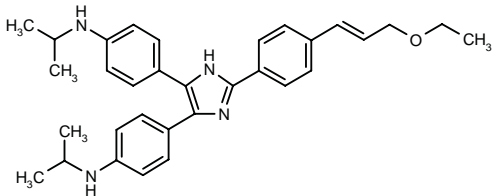
*Identified compound **221218** Drug Data Rep 1995, 017(07): 0668.

MODULATORS OF THE THERAPEUTIC
ACTIVITY OF ANTINEOPLASTIC
AGENTS

OC-144-093

272033

N-[4-[2-[4-[3-Ethoxy-1(*E*)-propenyl]phenyl]-4-[4-(isopropylamino)phenyl]-1*H*-imidazol-5-yl]phenyl]-*N*-isopropylamine



C32 H38 N4 O; Mol wt: 494.6792

ACTION – Multidrug resistance (MDR) modulator, a P-glycoprotein (P-gp) inhibitor (IC₅₀ = 30 nM) able to reverse MDR to doxorubicin, paclitaxel and vinblastine in human lymphoma, breast, ovarian, uterine and colorectal carcinoma cell lines expressing P-gp, with an average EC₅₀ value of 32 nM and associated with complete MDR reversal in the 0.25-1 μM range. The activity of compound persisted for up to 24 h after washout. It was not cytotoxic by itself at doses up to 100 μM and appeared to act by blocking the binding of [³H]-azidopine to P-gp and to inhibit P-gp ATPase activity. Compound exhibited high oral bioavailability in rodents and dogs (> 50%) and did not modify the pharmacokinetic profile of i.v. paclitaxel. *In vivo*, almost complete reversal of doxorubicin resistance in mice bearing MDR P388 leukemia cells was seen at 20 mg/kg p.o., and it significantly enhanced the antitumor activity of paclitaxel in mice bearing breast and colon carcinoma cells at 30 mg/kg p.o. Compound is undergoing phase I clinical trials.

SOURCE – Ontogen.

REFERENCES

1. Mjalli, A.M.M. and Zhang, C. (Ontogen Corp.) *Imidazole derivs. as MDR modulators*. EP 0999835, US 5840721, WO 9902155.

2. Dixon, R. and Toyonaga, B. *P-glycoprotein inhibitor OC144-093: Phase 1 intravenous and oral pharmacokinetics of a novel multidrug resistance modulator*. Proc Amer Assoc Cancer Res 2000, 41: Abst 3863.

3. Dixon, R. et al. *P-glycoprotein inhibitor OC144-093: Clinical pharmacokinetics and safety in healthy men following intravenous and oral dosing*. Annu Meet Am Assoc Pharm Sci (AAPS) (Nov 14-18, New Orleans) 1999, Abst 2027.

4. Luján, M. et al. *P-glycoprotein inhibitor OC144-093: Phase I oral safety and pharmacokinetics of a novel multidrug resistance modulator*. 7th World Conf Clin Pharmacol Ther (July 15-20, Florence) 2000, Abst 967.

5. Newman, M.J. et al. *Discovery and characterization of OC144-093, a novel inhibitor of P-glycoprotein-mediated multidrug resistance*. Cancer Res 2000, 60(11): 2964.

6. Newman, M.J. et al. *Discovery and characterization of OC144-093, a novel inhibitor of P-glycoprotein-mediated multidrug resistance*. Proc Amer Assoc Cancer Res 1999, 40: Abst 2080.

7. Newman, M.J. et al. *Novel in vivo mechanism of action and lack of pharmacokinetic interaction with plasma paclitaxel by the P-glycoprotein inhibitor OC144-093*. Proc Amer Assoc Cancer Res 2000, 41: Abst 2529.

8. Newman, M.J. et al. *Preclinical characterization and clinical safety/pharmacokinetics of OC144-093, a novel inhibitor of P-glycoprotein-mediated multidrug resistance*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 731.

9. *Ontogen completes phase I bioavailability study of MDR compound*. DailyDrugNews.com (Daily Essentials) 1999, Aug 3.

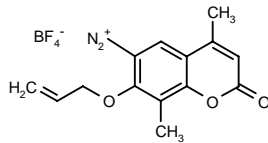
10. *Ontogen completes phase I multidose oral study of MDR compound*. DailyDrugNews.com (Daily Essentials) 1999, Nov 17.

11. *Ontogen completes phase I study of MDR compound*. DailyDrugNews.com (Daily Essentials) 1999, Feb 3.

PHOTOSENSITIZERS

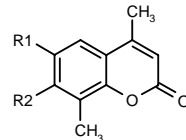
290973

7-Allyloxy-4,8-dimethyl-2-oxo-2*H*-1-benzopyran-6-diazonium tetrafluoroborate



C14 H13 B F4 N2 O3; Mol wt: 344.0707

ACTION – A representative compound from a series of 4'-substituted-4',5'-dihydropсорalen derivatives useful as photochemotherapeutic agents for the treatment of proliferative disorders, blood or bone marrow disorders and microbial infections; the compounds are reported to exhibit the advantage over previous psoralens of being unable to form crosslinks in DNA, resulting in reduced mutagenic/carcinogenic potential. *In vitro*, compound was shown to inhibit the growth of keratinocyte PAM212 cells following exposure to UVA light with an IC₅₀ value of 0.1 μM, while it was inactive (IC₅₀ > 100 μM) in the absence of light irradiation. Other exemplified compounds include the following:



Compound	R1	R2	Formula
290974	NO2	allyl-O	C ₁₄ H ₁₃ NO ₅
290975	-CH(CH ₂ CN)CH ₂ O-		C ₁₅ H ₁₃ NO ₃

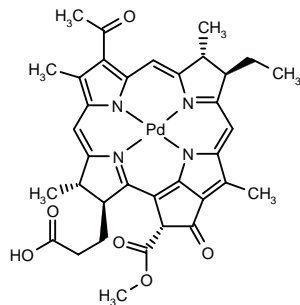
SOURCE – Buckman Laboratories.

REFERENCES

1. Heindel, N.D. et al. (Buckman Laboratories International, Inc.) *4'-Substd.-4',5'-dihydropсорalens and therapeutical uses thereof*. WO 0032603.

291143

Hydrogen (SP-4-2)-[(3*S*,4*S*,13*R*,14*R*,21*R*)-9-acetyl-14-ethyl-13,14-dihydro-21-(methoxycarbonyl)-4,8,13,18-tetramethyl-20-oxo-3-phorbinepropanoato(3-)-κ*N*²³,κ*N*²⁴,κ*N*²⁵,κ*N*²⁶]palladate(1-)



C35 H36 N4 O6 Pd; Mol wt: 715.1114

ACTION – Photosensitizing agent for use in the photodynamic therapy of tumors, also reported to be useful for the *in vitro* photodynamic killing of microorganisms. *In vitro*, compound exhibited cytotoxicity following light irradiation against several cancer cell lines including human bladder carcinoma ECV304 (LC₅₀ = 19 nM), murine melanoma M2R (LC₅₀ = 0.03 μM) and human colon adenocarcinoma HT29 (LC₅₀ = 0.5 μM), while *in vivo* it produced significant tumoricidal effects in murine tumor models following i.v. administration. A representative compound from a series of palladium-substituted bacteriochlorophyll derivatives.

SOURCE – Yeda.

REFERENCES

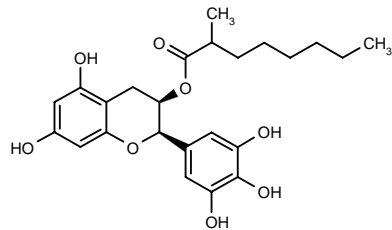
1. Scherz, A. et al. (Yeda Research & Development Co. Ltd.) *Palladium-substd. bacteriochlorophyll derivs. and use thereof*. WO 0033833.

CHEMOPREVENTIVE AGENTS

291934

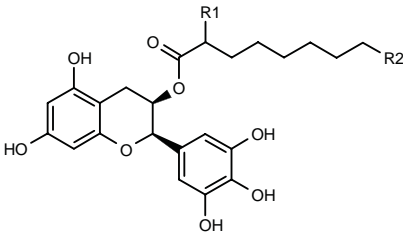
2-Methyloctanoic acid (2*R*,3*R*)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2*H*-1-benzopyran-3-yl ester

3-*O*-(2-Methyloctanoyl)epigallocatechin



C24 H30 O8; Mol wt: 446.4930

ACTION – Potential chemopreventive agent proven to inhibit the activation of Epstein-Barr virus early antigen (EBV-EA) induced by TPA in Raji cells, with improved potency compared to the parent compound (-)-epigallocatechin. Within this series of 3-*O*-acyl(-)-epigallocatechins, the following are also described:



Compound	R1	R2	Formula
291932	H	H	C ₂₃ H ₂₈ O ₈
291933	H	Et	C ₂₅ H ₃₂ O ₈
291935	Me	Et	C ₂₆ H ₃₄ O ₈

SOURCE – Mitsui Norin.

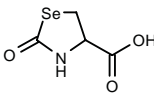
REFERENCES

1. Uesato, S. et al. *Antitumor promoting activities of 3-O-acyl(-)-epigallocatechins*. Bioorg Med Chem Lett 2000, 10(15): 1673.

OSCA

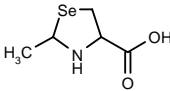
292492

2-Oxoselenazolidine-4-carboxylic acid



C4 H5 N O3 Se; Mol wt: 194.0475

ACTION – Chemopreventive agent, a selenazolidine prodrug proven to provide selenium (as the latent form of selenocysteine) at therapeutic levels without toxicity. Another related compound is:



MSCA [292493]: C5 H9 N O2 Se

SOURCE – University of Utah, Salt Lake City, UT (US).

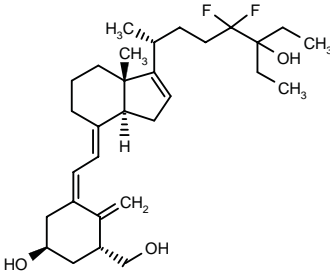
REFERENCES

1. Roberts, J.C. et al. *Selenium supplementation and cancer chemoprevention*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 193.

QW-1624F2-2

287532

(+)-(1α,3β)-24,24-Difluoro-25-hydroxy-1-(hydroxymethyl)-26,27-dimethyl-16,17-didehydrovitamin D₃



C30 H46 F2 O3; Mol wt: 492.6864

ACTION – Chemopreventive agent, a hybrid analogue of 1 α ,25-dihydroxyvitamin D₃ (calcitriol) that retains the latter’s potent antiproliferative and prodifferentiating activities but lacks the hypercalcemic activity. The antiproliferative activity of compound was equal to that of calcitriol in keratinocytes, but superior in murine malignant melanoma B15 cells. In rat osteosarcoma ROS 17/2.8 cells, it exhibited superior trascriptional activity compared to calcitriol (ED₅₀ = 0.05 and 0.3 nM, respectively). *In vivo* in rats, compound did not induce elevations in urinary calcium, in contrast to calcitriol, and no suppression of body weight gain was seen after treatment for 7 consecutive days.

SOURCE – Johns Hopkins University, Baltimore, MD (US).

REFERENCES

1. Posner, G.H. et al. (Johns Hopkins University) *Non-calcemic, antiproliferative, transcriptionally active 24-fluorinated hybrid analogs of 1 α ,25-dihydroxyvitamin D₃*. US 6043386.

2. Posner, G.H. *Exploratory studies on cancer chemoprevention using the natural hormone 1 α ,25-dihydroxyvitamin D₃, the phytochemical sulphoraphane and especially its synthetic analogs*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 191.

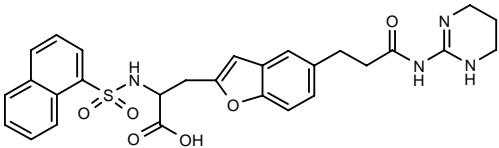
3. Posner, G.H. et al. *Noncalcemic, antiproliferative, transcriptionally active, 24-fluorinated hybrid analogues of the hormone 1 α ,25-dihydroxyvitamin D₃*. *Synthesis and preliminary biological evaluation*. J Med Chem 1998, 41(16): 3008.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

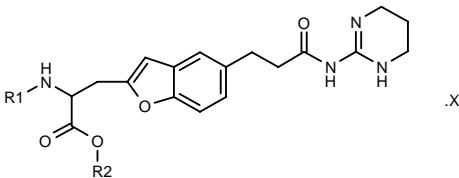
290526

2-(1-Naphthylsulfonamido)-3-[5-[3-oxo-3-(1,4,5,6-tetrahydropyrimidin-2-ylamino)propyl]benzofuran-2-yl]propionic acid



C28 H28 N4 O6 S; Mol wt: 548.6172

ACTION – Agent for the treatment or prevention of bone disorders, particularly osteoporosis, hypercalcemia, osteopenia, dental disorders, hyperparathyroidism, peri-articular erosion in rheumatoid arthritis and Paget's disease, as well as cancer, inflammatory disorders, cardiovascular diseases, nephropathies and retinopathies, a vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist and inhibitor of osteoclast-mediated bone resorption. *In vitro*, compound inhibited kistrin binding to the human vitronectin receptor with an IC₅₀ value of 0.0055 μ M. Other specifically claimed compounds from this series of benzofurane derivatives include the following:



Compound	R1	R2	X	Formula
290527	CO2CH2Ph	H		C ₂₆ H ₂₈ N ₄ O ₆
290528	1-adamantyl-CH2OCO	H	CF3CO2H	C ₃₀ H ₃₈ N ₄ O ₆ .C ₂ HF ₃ O ₂
290529	1-adamantyl-CH2OCONHSO2	H		C ₃₀ H ₃₈ N ₅ O ₆ S
290530	SO2NHCO2CH2Ph	H		C ₂₆ H ₂₈ N ₅ O ₆ S
290531	SO2NHCH2Ph	H		C ₂₅ H ₂₈ N ₅ O ₆ S
290532	1-Naph-SO2	i-Pr		C ₃₁ H ₃₄ N ₄ O ₆ S
290534	4-t-Bu-PhSO2	H		C ₂₈ H ₃₄ N ₄ O ₆ S
290535	4-i-Pr-PhSO2	H		C ₂₇ H ₃₂ N ₄ O ₆ S
290536	SO2Pr	H		C ₂₁ H ₂₈ N ₄ O ₆ S
290537	SO2Me	H		C ₁₉ H ₂₄ N ₄ O ₆ S

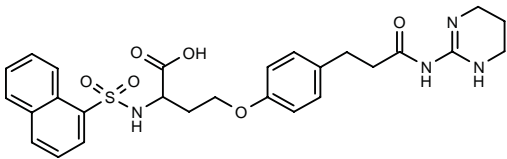
SOURCES – Aventis Pharma; Genentech.

REFERENCES

1. Carniato, D. et al. (Aventis Pharma SA;Genentech, Inc.) *Novel benzofurane derivs., preparation method, use as medicines and pharmaceutical compsns. containing same*. FR 2786184, WO 0031070.

290538

2-(1-Naphthylsulfonamido)-4-[4-[3-oxo-3-(1,4,5,6-tetrahydropyrimidin-2-ylamino)propyl]phenoxy]butyric acid



C27 H30 N4 O6 S; Mol wt: 538.6220

ACTION – Agent for the treatment or prevention of bone disorders, particularly osteoporosis, hypercalcemia, osteopenia, dental disorders, hyperparathyroidism, periarticular erosion in rheumatoid arthritis and Paget’s disease, as well as cancer, inflammatory disorders, cardiovascular diseases, nephropathies and retinopathies, a vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist and inhibitor of osteoclast-mediated bone resorption. *In vitro*, compound inhibited kistrin binding to the human vitronectin receptor with an IC₅₀ value of 0.0025 μ M. Other specifically claimed compounds from this series of acylguanidine derivatives are:

ACTION – Chemopreventive agent, a hybrid analogue of 1 α ,25-dihydroxyvitamin D₃ (calcitriol) that retains the latter’s potent antiproliferative and prodifferentiating activities but lacks the hypercalcemic activity. The antiproliferative activity of compound was equal to that of calcitriol in keratinocytes, but superior in murine malignant melanoma B15 cells. In rat osteosarcoma ROS 17/2.8 cells, it exhibited superior trascriptional activity compared to calcitriol (ED₅₀ = 0.05 and 0.3 nM, respectively). *In vivo* in rats, compound did not induce elevations in urinary calcium, in contrast to calcitriol, and no suppression of body weight gain was seen after treatment for 7 consecutive days.

SOURCE – Johns Hopkins University, Baltimore, MD (US).

REFERENCES

1. Posner, G.H. et al. (Johns Hopkins University) *Non-calcemic, antiproliferative, transcriptionally active 24-fluorinated hybrid analogs of 1 α ,25-dihydroxyvitamin D₃*. US 6043386.

2. Posner, G.H. *Exploratory studies on cancer chemoprevention using the natural hormone 1 α ,25-dihydroxyvitamin D₃, the phytochemical sulphoraphane and especially its synthetic analogs*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 191.

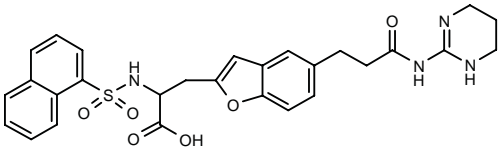
3. Posner, G.H. et al. *Noncalcemic, antiproliferative, transcriptionally active, 24-fluorinated hybrid analogues of the hormone 1 α ,25-dihydroxyvitamin D₃*. *Synthesis and preliminary biological evaluation*. J Med Chem 1998, 41(16): 3008.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

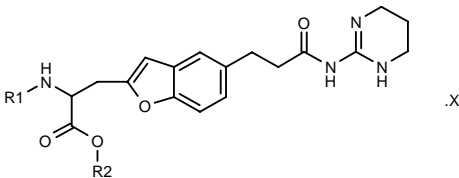
290526

2-(1-Naphthylsulfonamido)-3-[5-[3-oxo-3-(1,4,5,6-tetrahydropyrimidin-2-ylamino)propyl]benzofuran-2-yl]propionic acid



C28 H28 N4 O6 S; Mol wt: 548.6172

ACTION – Agent for the treatment or prevention of bone disorders, particularly osteoporosis, hypercalcemia, osteopenia, dental disorders, hyperparathyroidism, peri-articular erosion in rheumatoid arthritis and Paget's disease, as well as cancer, inflammatory disorders, cardiovascular diseases, nephropathies and retinopathies, a vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist and inhibitor of osteoclast-mediated bone resorption. *In vitro*, compound inhibited kistrin binding to the human vitronectin receptor with an IC₅₀ value of 0.0055 μ M. Other specifically claimed compounds from this series of benzofurane derivatives include the following:



Compound	R1	R2	X	Formula
290527	CO2CH2Ph	H		C ₂₆ H ₂₈ N ₄ O ₆
290528	1-adamantyl-CH2OCO	H	CF3CO2H	C ₃₀ H ₃₈ N ₄ O ₆ .C ₂ HF ₃ O ₂
290529	1-adamantyl-CH2OCONHSO2	H		C ₃₀ H ₃₈ N ₅ O ₆ S
290530	SO2NHCO2CH2Ph	H		C ₂₆ H ₂₈ N ₅ O ₆ S
290531	SO2NHCH2Ph	H		C ₂₅ H ₂₈ N ₅ O ₆ S
290532	1-Naph-SO2	i-Pr		C ₃₁ H ₃₄ N ₄ O ₆ S
290534	4-t-Bu-PhSO2	H		C ₂₈ H ₃₄ N ₄ O ₆ S
290535	4-i-Pr-PhSO2	H		C ₂₇ H ₃₂ N ₄ O ₆ S
290536	SO2Pr	H		C ₂₁ H ₂₈ N ₄ O ₆ S
290537	SO2Me	H		C ₁₉ H ₂₄ N ₄ O ₆ S

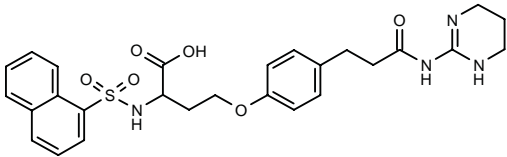
SOURCES – Aventis Pharma; Genentech.

REFERENCES

1. Carniato, D. et al. (Aventis Pharma SA;Genentech, Inc.) *Novel benzofurane derivs., preparation method, use as medicines and pharmaceutical compsns. containing same*. FR 2786184, WO 0031070.

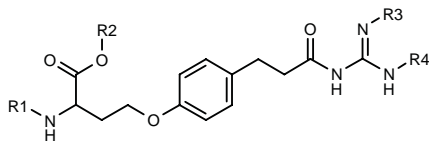
290538

2-(1-Naphthylsulfonamido)-4-[4-[3-oxo-3-(1,4,5,6-tetrahydropyrimidin-2-ylamino)propyl]phenoxy]butyric acid

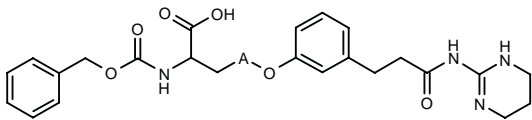


C27 H30 N4 O6 S; Mol wt: 538.6220

ACTION – Agent for the treatment or prevention of bone disorders, particularly osteoporosis, hypercalcemia, osteopenia, dental disorders, hyperparathyroidism, periarticular erosion in rheumatoid arthritis and Paget’s disease, as well as cancer, inflammatory disorders, cardiovascular diseases, nephropathies and retinopathies, a vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist and inhibitor of osteoclast-mediated bone resorption. *In vitro*, compound inhibited kistrin binding to the human vitronectin receptor with an IC₅₀ value of 0.0025 μ M. Other specifically claimed compounds from this series of acylguanidine derivatives are:



Compound	R1	R2	R3	R4	Formula
290539	CO2CH2Ph	H	H	H	C ₂₂ H ₂₆ N ₄ O ₆
290540	CO2CH2Ph	H	-(CH2)3-		C ₂₅ H ₃₀ N ₄ O ₆
290541	CO2CH2Ph	Et	-(CH2)3-		C ₂₇ H ₃₄ N ₄ O ₆
290542	CO2CH2Ph	i-Pr	-(CH2)3-		C ₂₈ H ₃₆ N ₄ O ₆
290543	1-adamantyl-CH2OCO	H	-(CH2)3-		C ₂₉ H ₄₀ N ₄ O ₆
290544	2,4,6-(Me)3-PhSO2	H	-(CH2)3-		C ₂₆ H ₃₄ N ₄ O ₆ S



Compound	A	Formula
290545	-CH2-	C ₂₅ H ₃₀ N ₄ O ₆
290546	-(CH2)2-	C ₂₆ H ₃₂ N ₄ O ₆

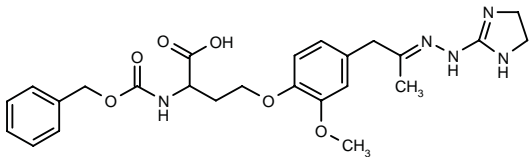
SOURCES – Aventis Pharma; Genentech.

REFERENCES

1. Carniato, D. et al. (Aventis Pharma SA;Genentech, Inc.) *Novel acylguanidine derivs., method for preparing same, application as medicines and pharmaceutical compsns. containing them.* FR 2786182, WO 0031046.

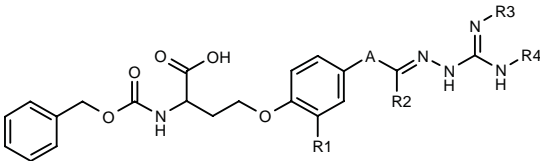
290547

2-(Benzyloxycarbonylamino)-4-[4-[2-[2-(4,5-dihydro-1 H-imidazol-2-yl)hydrazono]propyl]-2-methoxyphenoxy]-butyric acid

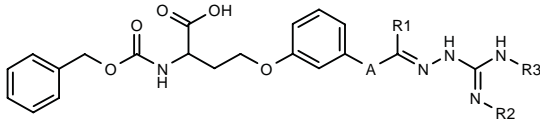


C25 H31 N5 O6; Mol wt: 497.5489

ACTION – Agent for the treatment or prevention of bone disorders, particularly osteoporosis, hypercalcemia, osteopenia, dental disorders, hyperparathyroidism, peri-articular erosion in rheumatoid arthritis and Paget’s disease, as well as cancer, inflammatory disorders, cardiovascular diseases, nephropathies and retinopathies, a vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist and inhibitor of osteoclast-mediated bone resorption. *In vitro*, compound inhibited kistrin binding to the human vitronectin receptor with an IC₅₀ value of 0.012 μ M. Other specifically claimed compounds from this series of iminoguanidine derivatives are:



Compound	R1	R2	R3	R4	A	Formula
290548	H	Me	-(CH2)2-		-(CH2)2-	C ₂₅ H ₃₁ N ₅ O ₅
290549	H	Me	H	H	-(CH2)2-	C ₂₃ H ₂₉ N ₅ O ₅
290550	H	H	-(CH2)2-		-(CH2)2-	C ₂₄ H ₂₉ N ₅ O ₅
290551	H	H	H	H	-(CH2)2-	C ₂₂ H ₂₇ N ₅ O ₅
290552	H	Me	-(CH2)2-		-CH2-	C ₂₄ H ₂₉ N ₅ O ₅
290553	F	Me	-(CH2)2-		-CH2-	C ₂₄ H ₂₈ FN ₅ O ₅
290559	H	H	-(CH2)2-		bond	C ₂₂ H ₂₅ N ₅ O ₅



Compound	R1	R2	R3	A	Formula
290554	Me	H	H	-(CH2)2-	C ₂₃ H ₂₉ N ₅ O ₅
290555	Me		-(CH2)2-	-(CH2)2-	C ₂₅ H ₃₁ N ₅ O ₅
290556	Me		-(CH2)2-	-CH2-	C ₂₄ H ₂₉ N ₅ O ₅
290557	H	H	H	-(CH2)2-	C ₂₂ H ₂₇ N ₅ O ₅
290558	H		-(CH2)2-	-(CH2)2-	C ₂₄ H ₂₉ N ₅ O ₅

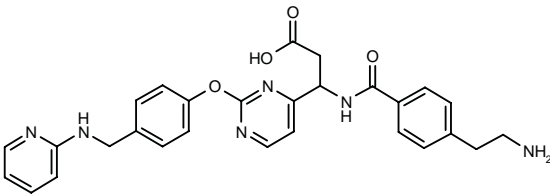
SOURCES – Aventis Pharma; Genentech.

REFERENCES

1. Carniato, D. et al. (Aventis Pharma SA;Genentech, Inc.) *Iminoguanidine derivs., preparation method, use as medicines.* FR 2786181, WO 0031044.

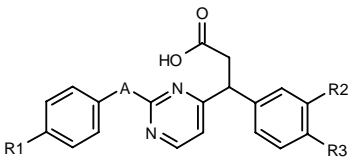
290694

3-[4-(2-Aminoethyl)benzamido]-3-[2-[4-(2-pyridinyl-aminomethyl)phenoxy]pyrimidin-4-yl]propionic acid



C28 H28 N6 O4; Mol wt: 512.5672

ACTION – Potent and selective inhibitor of α_v integrins such as $\alpha_v\beta_3$ and $\alpha_v\beta_5$, with potential in the treatment of conditions involving inappropriate growth or migration of cells such as tumor growth and metastasis, retinopathy, macular degeneration, psoriasis, rheumatoid arthritis, osteoporosis, Paget’s disease, hyperparathyroidism, periodontal disease, vascular restenosis, athero-sclerosis and inflammatory bowel disease. A representative compound from a series of propanoic acid derivatives, wherein the following are also specifically claimed:



Compound	R1	R2	R3	A	Formula
290697	4,5-dihydro-2-imidazolyl-NHCH2	H	F	-O-	C ₂₃ H ₂₂ FN ₅ O ₃
290699	CH2NHC(=NH)NH2	H	CO2H	-O-	C ₂₂ H ₂₁ N ₅ O ₅
290702	CH2NHC(=NH)NH2	H	F	-N(Me)-	C ₂₂ H ₂₃ FN ₆ O ₂
290704	2-Pyr-NHCH2	OMe	H	-O-	C ₂₆ H ₂₄ N ₄ O ₄
290705	6-NH2-2-Pyr	H	CO2H	-O-	C ₂₅ H ₂₀ N ₄ O ₅
290706	6-MeNH-2-Pyr	H	CO2H	-O-	C ₂₆ H ₂₂ N ₄ O ₅
290707	2-benzimidazolyl-NHCH2	H	F	-O-	C ₂₇ H ₂₂ FN ₅ O ₃
290708	2-Pyr-NHCH2	CO2H	H	-O-	C ₂₆ H ₂₂ N ₄ O ₅

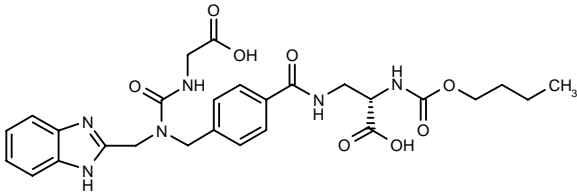
SOURCE – Celltech Group.

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1. Alexander, R.P. et al. (Celltech Chiroscience plc) *Propanoic acid derivs. as integrin inhibitors*. WO 0031067.

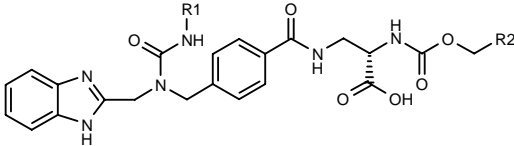
290750

3-[4-[1-(1*H*-Benzimidazol-2-ylmethyl)-3-(carboxymethyl)-ureidomethyl]benzamido]-2(*S*)-(butoxycarbonylamino)-propionic acid



C27 H32 N6 O8; Mol wt: 568.5838

ACTION – Vitronectin receptor antagonist with selectivity for the $\alpha_v\beta_3$ receptor, giving an IC₅₀ of 4.3 nM for inhibition of echistatin binding to integrin $\alpha_v\beta_3$ receptors and a specificity index (IC₅₀ for gpIIb/IIIa/IC₅₀ for $\alpha_v\beta_3$) of 2,600 in competition radioligand binding assays. It is expected to be of use for the treatment of vitronectin-mediated disorders such as cancer, retinopathy, atherosclerosis, vascular restenosis and osteoporosis. Other specifically claimed benzimidazole compounds include the following:



Compound	R1	R2	Formula
290752	4-F-Ph	Ph	C ₃₄ H ₃₁ FN ₆ O ₆
290753	CH2CO2Et	Ph	C ₃₂ H ₃₄ N ₆ O ₈
290755	cyclohexyl	Ph	C ₃₄ H ₃₈ N ₆ O ₆
290756	CH2CO2H	Ph	C ₃₀ H ₃₀ N ₆ O ₈
290757	Ph	Ph	C ₃₄ H ₃₂ N ₆ O ₆
290758	Ph	Pr	C ₃₁ H ₃₄ N ₆ O ₆
290770	CH2CO2Et	Pr	C ₂₉ H ₃₆ N ₆ O ₈

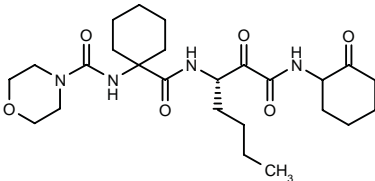
SOURCE – Schering-Plough.

REFERENCES

1. Neustadt, B.R. and Smith, E.M. (Schering Corp.) *Benzimidazole cpds. that are vitronectin receptor antagonists*. WO 0032578.

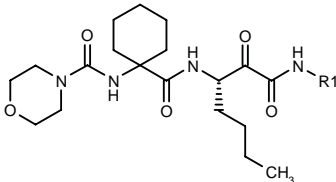
290893

N-[1-[*N*-[1(*S*)-[2-Oxo-2-(2-oxocyclohexylamino)acetyl]-pentyl]carbamoyl]cyclohexyl]morpholine-4-carboxamide



C25 H40 N4 O6; Mol wt: 492.6130

ACTION – Selective cathepsin K inhibitor (99% inhibition at 1 μ M) with potential in the treatment of bone disorders such as osteoporosis, hypercalcemia and Paget's disease, as well as rheumatoid arthritis. *In vivo*, compound was shown to inhibit bone resorption in mice fed a low-calcium diet when dosed at 100 mg/kg p.o. In addition, it was shown to induce a significant recovery of bone mineral density and strength, as well as a significant decrease in urine deoxypyridinoline, a bone resorption marker, in an ovariectomized rat model of osteoporosis at 100 mg/kg/day p.o. b.i.d. for 12 weeks. Other exemplified compounds from this series of cyclic amide derivatives include the following:



Compound	R1	Formula
290894	1-(2-t-Bu-1,3-dioxolan-2-yl)-CH2	C ₂₇ H ₄₆ N ₄ O ₇
290895	(<i>S</i>)-CH(Ph)CO2Me	C ₂₈ H ₄₀ N ₄ O ₇

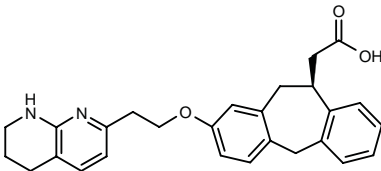
SOURCE – UCB Japan.

REFERENCES

1. Hosoda, A. et al. (UCB Japan) *Cyclic amide derivs. which inhibit cathepsin K*. EP 1008592, JP 2000204071, US 6117870.

291142

2-[2-[2-(5,6,7,8-Tetrahydro[1,8]naphthyridin-2-yl)ethoxy]-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-10(*S*)-yl]acetic acid



C27 H28 N2 O3; Mol wt: 428.5292

ACTION – Vitronectin $\alpha_v\beta_3$ receptor antagonist (K_i about 1.7 nM for inhibiting SK&F-107260 binding to vitronectin) for the treatment of bone resorption-associated diseases such as osteoporosis and osteoarthritis. Its use in the treatment of inflammation, cancer and cardiovascular disorders such as atherosclerosis and restenosis is also specifically claimed.

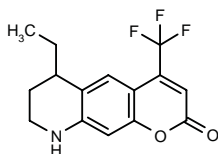
SOURCE – SmithKline Beecham.

REFERENCES

1. Miller, W.H. and Manley, P.J. (SmithKline Beecham Corp.) *Vitronectin receptor antagonist*. WO 0033838.

291314

(–)-6-Ethyl-4-(trifluoromethyl)-6,7,8,9-tetrahydro-2H-pyrano[3,2-g]quinolin-2-one



C15 H14 F3 N O2; Mol wt: 297.2746

ACTION – Agent for the treatment of frailty, osteoporosis or wasting diseases, the (–)-enantiomer of an androgen receptor modulator previously known in racemate form. This enantiomer exhibits higher affinity for the human androgen receptor (hAR), as demonstrated in a binding assay using recombinant hAR by an IC_{50} value of 5 nM versus IC_{50} values of 35 nM for the racemate and 112 nM for the (+)-enantiomer.

SOURCE – Pfizer.

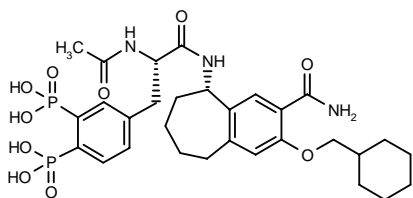
REFERENCES

1. Gant, T.G. (Pfizer Inc.) *Optically pure androgen mediator*. JP 2000159771, US 6083956.

AP-22408

292485

4-[2(S)-(Acetamido)-3-[3-(aminocarbonyl)-2-(cyclohexylmethoxy)-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5(S)-ylamino]-3-oxopropyl]benzene-1,2-diphosphonic acid



C30 H41 N3 O10 P2; Mol wt: 665.6129

ACTION – Nonpeptide inhibitor of the protein tyrosine kinase Src homology 2 domain (SH2; IC_{50} = 5.5 μ M) with strong bone affinity, able to accumulate at high levels on the bone surface and to strongly inhibit osteoclast-mediated bone resorption in a cellular assay (IC_{50} = 1.6 μ M). *In vivo*, in a model of parathyroid hormone-induced bone resorption using thyroparathyroidectomized rats, compound given at a dose of 50 mg/kg i.p. twice daily for 18 days exhibited a statistically significant antiresorptive effect.

SOURCE – Ariad.

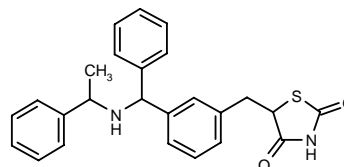
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1. Shakespeare, W.C. et al. (Ariad Pharmaceuticals Inc.) *Bicyclic signal transduction inhibitors, compsns. containing them & uses thereof*. WO 0027802.
2. Shakespeare, W. et al. *Structure-based design of an osteoclast-selective, nonpeptide Src homology 2 inhibitor with in vivo antiresorptive activity*. Proc Natl Acad Sci USA 2000, 97(17): 9373.
3. *Ariad updates stockholders*. DailyDrugNews.com (Daily Essentials) 1998, Sept 9.

TREATMENT OF LIPOPROTEIN DISORDERS

291435

5-[3-[1-Phenyl-1-(1-phenylethylamino)methyl]benzyl]-thiazolidine-2,4-dione



C25 H24 N2 O2 S; Mol wt: 416.5426

ACTION – Agent for the treatment of hyperlipidemia and arteriosclerosis, an inhibitor of ileoileal bile acid transport, as demonstrated by inhibition of [3 H]-taurocholate uptake both in Caco-2 cells expressing the bile acid transporter (IC_{50} = 0.59 μ g/ml) and in hamster everted ileal rings (61.87% inhibition at 100 μ g/ml). A representative compound from a series of substituted benzylamines.

SOURCE – Sankyo.

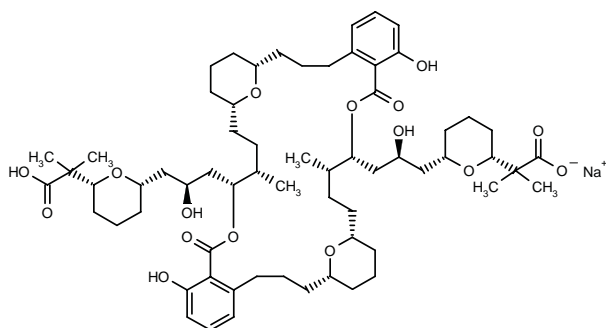
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1. Ishihara, S. et al. (Sankyo Co., Ltd.) *Substd. benzylamines*. JP 2000229958, WO 0035889.

SCH-351448

288083

(2*R*,2'*R*,6*S*,6'*S*)-6,6'-[(7*R*,8*S*,11*S*,15*S*,25*R*,26*S*,29*S*,33*S*)-4,22-Dihydroxy-8,26-dimethyl,5,23-dioxo-11,15:29,33-diepoxy-5,7,8,9,10,11,12,13,14,15,16,17,18,23,25,26,27,28,29,30,31,32,33,34,35,36-hexacosahydrodibenzo[*c,s*][1,17]dioxacyclodotriacontin-7,25-diyl]bis[2(*S*)-hydroxy-3,1-propanediyl]bis[α,α -dimethyltetrahydro-2*H*-pyran-2-acetic acid monosodium salt]



C64 H95 Na O16; Mol wt: 1143.4280

ACTION – Selective activator of the LDL receptor promoter, a microbial metabolite extracted from a fermentation broth of a *Micromonospora* sp., giving an ED₅₀ value of 25 μ M in an LDL receptor promoter transcription assay using human growth hormone (hGH) as a reporter gene. It did not activate the transcription of hGH from the SR α promoter. Compound is expected to decrease serum LDL levels by increasing LDL uptake by the LDL receptor and thus represents a potential treatment for lipoprotein disorders.

SOURCE – Schering-Plough.

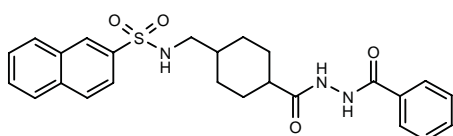
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1. Hegde, V.R. et al. A novel microbial metabolite, activator of low density lipoprotein receptor promoter. Tetrahedron Lett 2000, 41(9): 1351.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

290999

N-[4-(2-Benzoylhydrazinocarbonyl)cyclohexylmethyl]-naphthalene-2-sulfonamide



C25 H27 N3 O4 S; Mol wt: 465.5713

ACTION – Agent with high affinity for neuropeptide Y (NPY) Y₅ receptors (IC₅₀ = 14.5 nM), proven to decrease food intake and body weight by 75.2 and 6.0%, respectively, when given at 5 mg/kg i.p. to *ob/ob* mice. Potentially useful for the treatment of eating or metabolic disorders such as diabetes, obesity, bulimia, anorexia, as well as in the treatment of arterial hypertension, anxiety, depression, epilepsy, sexual dysfunction and sleep disorders. A representative compound from a series of hydrazide derivatives.

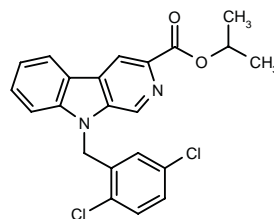
SOURCE – ADIR.

REFERENCES

1. Monge Vega, A. et al. (ADIR et Cie.) Hydrazide derivs., process for their preparation and pharmaceutical compsns. containing them. EP 1010691, JP 2000178240.

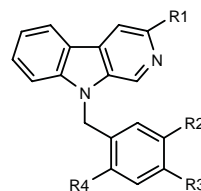
291323

9-(2,5-Dichlorobenzyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid isopropyl ester

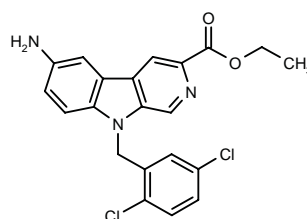


C22 H18 Cl2 N2 O2; Mol wt: 413.3022

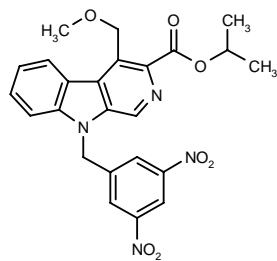
ACTION – Nonpeptide glucagon-like peptide 1 (GLP-1) antagonist that provides better biodistribution and tolerance to physiological degradation than peptide GLP-1 modulators. Antagonists of GLP-1 may be of use to increase eating in disorders characterized by cachexia and for the treatment of postprandial hypoglycemia and the dumping syndrome. Other nonpeptide GLP-1 antagonists include the following:



Compound	R1	R2	R3	R4	Formula
291324	CO2Pr	Cl	H	Cl	C ₂₂ H ₁₈ Cl ₂ N ₂ O ₂
291327	4-morpholinyl-CH ₂ CH ₂ OCO	H	Cl	Cl	C ₂₈ H ₂₃ Cl ₂ N ₃ O ₃
291328	4-morpholinyl-CH ₂ CH ₂ OCO	H	CF ₃	CF ₃	C ₂₇ H ₂₃ F ₆ N ₃ O ₃
291329	4-CO ₂ H-PhCH=NNHCO	Cl	H	Cl	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₃
291330	CO ₂ Et	Cl	H	Cl	C ₂₁ H ₁₆ Cl ₂ N ₂ O ₂
291331	cis-4-CN-cyclohexyl-CH ₂ N(COCH ₂ OAe)CH ₂	Cl	H	Cl	C ₃₁ H ₃₀ Cl ₂ N ₄ O ₃



291325: C21 H17 Cl2 N3 O2



291326: C24 H22 N4 O7

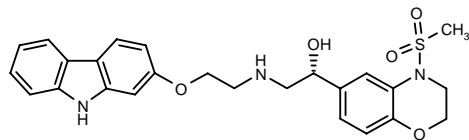
SOURCE – Agouron (Pfizer).

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1. Truesdale, L.K. et al. (Agouron Pharmaceuticals, Inc.) *Non-peptide antagonists of GLP-1 receptor and methods of use.* WO 0033839.

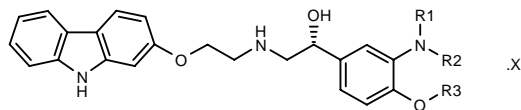
291422

2-[2-(9*H*-Carbazol-2-yloxy)ethylamino]-1-[4-(methylsulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl]ethan-1(*R*)-ol



C25 H27 N3 O5 S; Mol wt: 481.5703

ACTION – Agent for the treatment of obesity, diabetes and hyperlipidemia, a β_3 -adrenoceptor agonist, as demonstrated by stimulation of cAMP in CHO cells transfected with the human β_3 -adrenoceptor (EC_{50} = 12 nM; 69% activation vs. isoproterenol), reported to possess good oral activity and low toxicity. Other compounds from this series of heterocyclic derivatives include the following:



Compound	R1	R2,R3	X	Formula
291424	SO2Me	-CH2-	D-tartrate	C ₂₄ H ₂₅ N ₃ O ₅ S.C ₄ H ₆ O ₆
291430	SO2Me	-(CH2)3-		C ₂₆ H ₂₉ N ₃ O ₅ S
291431	SO2N(Me)2	-(CH2)2-		C ₂₆ H ₃₀ N ₄ O ₅ S
291432	SO2N(Me)2	-CO-	HCl	C ₂₅ H ₂₆ N ₄ O ₆ S.HCl
291433	SO2N(Me)2	-CS-	HCl	C ₂₅ H ₂₆ N ₄ O ₅ S ₂ .HCl
291434	H	-CO-	HCl	C ₂₃ H ₂₁ N ₃ O ₄ .HCl

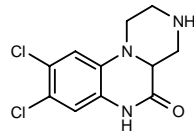
SOURCE – Asahi Chemical.

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1. Miyoshi, S. and Ogawa, K. (Asahi Chemical Industry Co., Ltd.) *Novel heterocyclic cpds. and drug compsns. containing the same.* WO 0035890.

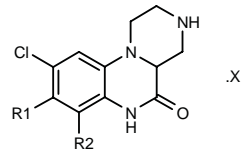
291590

8,9-Dichloro-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]-quinoxalin-5-one



C11 H11 Cl2 N3 O; Mol wt: 272.1339

ACTION – 5-HT_{2C} receptor agonist giving a K_i value of 4.33 nM in a 5-HT_{2C} receptor binding test and shown to stimulate [³H]-inositol monophosphate production with an EC_{50} of 12.00 nM, both in CHO cells. The compound was also found to reduce food intake in rats fasted for 24 h, with ED50 values of 1.91 mg/kg i.p. and 9.73 mg/kg p.o. Potentially useful for the treatment of obsessive-compulsive disorder, depression, anxiety, schizophrenia, migraine, sleep disorders, eating disorders, obesity, type 2 diabetes and epilepsy. Other exemplified 2,3,4,4a-tetrahydro-1*H*-pyrazino[1,2-*a*]quinoxalin-5(6*H*)-one derivatives include the following:



Compound	R1	R2	X	Isomer	Formula
291591	Cl	H		R	C ₁₁ H ₁₁ Cl ₂ N ₃ O
291592	H	Cl	HCl		C ₁₁ H ₁₁ Cl ₂ N ₃ O.HCl

SOURCE – American Home Products.

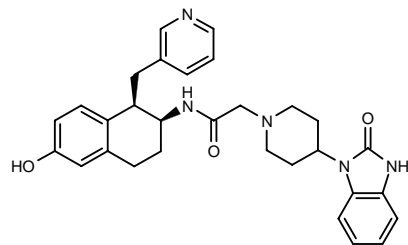
REFERENCES

1. Sabb, A.L. et al. (American Home Products Corp.) *2,3,4,4a-Tetrahydro-1H-pyrazino[1,2-a]quinoxalin-5(6H)one derivates being 5HT_{2C} agonists.* WO 0035922.

2. Welmaker, G.S. et al. *Synthesis and 5-hydroxytryptamine (5-HT) activity of 2,3,4,4a-tetrahydro-1H-pyrazino[1,2-a]quinoxalin-5-(6H)ones and 2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a]quinoxalines.* Bioorg Med Chem Lett 2000, 10(17): 1991.

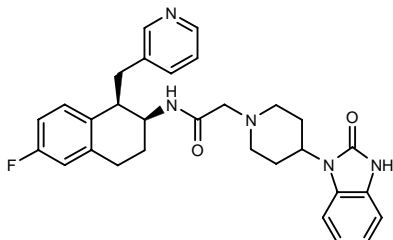
291927

N-[*cis*-6-Hydroxy-1-(3-pyridinylmethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-2-[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]acetamide



C30 H33 N5 O3; Mol wt: 511.6227

ACTION – High-affinity human neuropeptide Y (NPY) Y_5 receptor ligand ($IC_{50} = 6$ nM) with functional antagonist activity, as demonstrated by inhibition of PYY-induced incorporation of ^{35}S -GTP γ S into membranes from Y_5 receptor-expressing HEK293 cells ($K_b = 20$ nM). Potentially useful for the treatment of obesity. Another related compound is:



291926: C30 H32 F N5 O2

SOURCE – R.W. Johnson.

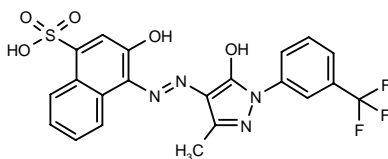
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HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

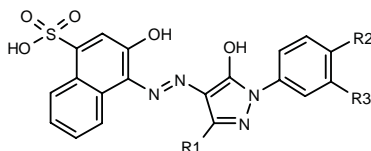
291537

3-Hydroxy-4-[2-[5-hydroxy-3-methyl-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl]diazenyl]naphthalene-1-sulfonic acid



C21 H15 F3 N4 O5 S; Mol wt: 492.4325

ACTION – Nonpeptide thrombopoietin mimetic that promotes thrombopoiesis and megakaryocytopoiesis and is useful for the treatment of thrombocytopenia and other conditions with depressed platelet production. Other compounds from this series of 1-azonaphthalene derivatives are:



Compound	R1	R2	R3	Formula
291538	Me	Me	Me	C ₂₂ H ₂₀ N ₄ O ₅ S
291539	Me	I	H	C ₂₆ H ₁₅ IN ₄ O ₅ S
291540	OEt	Me	Me	C ₂₃ H ₂₂ N ₄ O ₅ S
291541	Me	CF3	H	C ₂₁ H ₁₅ F ₃ N ₄ O ₅ S

SOURCES – Ligand; SmithKline Beecham.

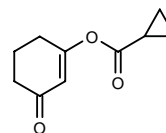
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1. Luengo, J.I. et al. (SmithKline Beecham Corp.;Ligand Pharmaceuticals, Inc.) *Thrombopoietin mimetics*. WO 0035446.

THERAPY OF INBORN ERRORS OF METABOLISM

290389

Cyclopropanecarboxylic acid 3-oxo-1-cyclohexenyl ester



C10 H12 O3; Mol wt: 180.2018

ACTION – Potent, low-molecular-weight inhibitor of 4-hydroxyphenylpyruvate dioxygenase ($IC_{50} = 30$ nM), potentially useful for the treatment of the fatal hereditary disease tyrosinemia type I, which leads to the accumulation of hepatotoxic and nephrotoxic compounds such as succinylacetone.

SOURCE – Tunghai Christian University, Taichung (TW).

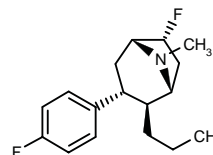
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TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

291274

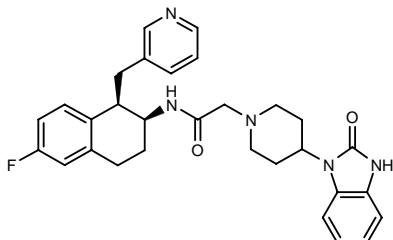
6*endo*-Fluoro-3*endo*-(4-fluorophenyl)-8-methyl-2*exo*-propyl-8-azabicyclo[3.2.1]octane



C17 H23 F2 N; Mol wt: 279.3717

ACTION – Dopamine transporter (DAT) inhibitor ($K_i = 30$ nM for displacing [3H]-mazindol binding to cocaine binding sites on DAT of rat striatal membranes; $K_i = 49$ nM for inhibition of dopamine reuptake) with comparable activity at the norepinephrine transporter ($K_i = 52$ nM) and poor activity at the 5-HT transporter ($K_i = 516$ nM). In behavioral experiments in rats, doses of 5-10 mg/kg i.p. reduced the rewarding effects of cocaine in the brain stimulation reward paradigm. Potentially useful for the treatment of cocaine abuse.

ACTION – High-affinity human neuropeptide Y (NPY) Y_5 receptor ligand ($IC_{50} = 6$ nM) with functional antagonist activity, as demonstrated by inhibition of PYY-induced incorporation of ^{35}S -GTP γ S into membranes from Y_5 receptor-expressing HEK293 cells ($K_b = 20$ nM). Potentially useful for the treatment of obesity. Another related compound is:



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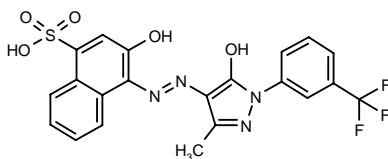
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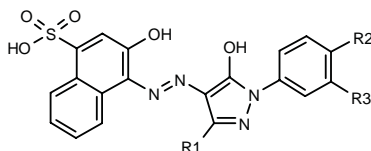
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SOURCES – Ligand; SmithKline Beecham.

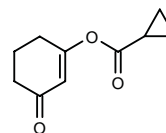
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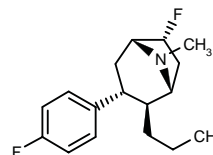
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291274

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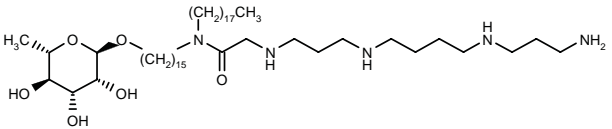
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DRUG DELIVERY

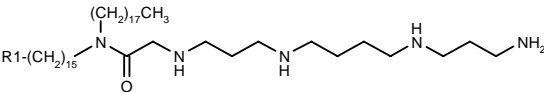
290731

2-[3-[4-(3-Aminopropylamino)butylamino]propylamino]-*N*-octadecyl-*N*-[15-(6-deoxy- α -L-mannopyranosyloxy)pentadecyl]acetamide



C51 H105 N5 O6; Mol wt: 884.4195

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SOURCE – Aventis Pharma.

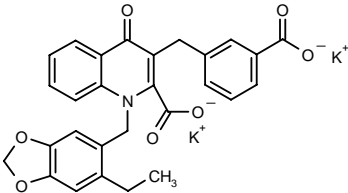
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PHARMACOLOGICAL TOOLS

291285

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GsMTX-4

291307

H-Gly-Cys-Leu-Glu-Phe-Trp-Trp-Lys-Cys-Asn-Pro-Asn-Asp-Asp-Lys-Cys-Cys-Arg-Pro-Lys-Leu-Lys-Cys-Ser-Lys-Leu-Phe-Lys-Leu-Cys-Asn-Phe-Ser-Ser-Ala-OH

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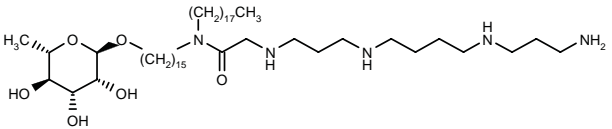
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DRUG DELIVERY

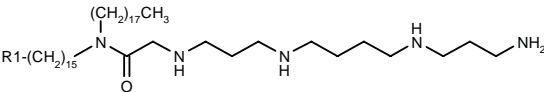
290731

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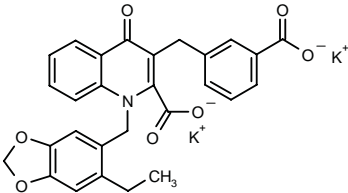
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GsMTX-4

291307

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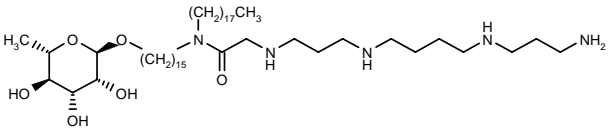
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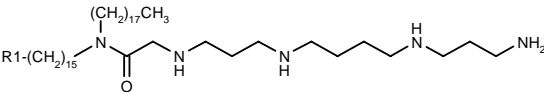
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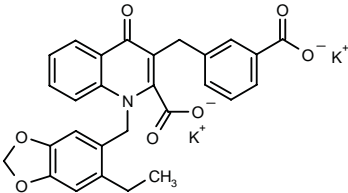
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SOURCES – Michigan State University, East Lansing, MI (US); NPS Pharmaceuticals; State University of New York, Buffalo, Buffalo, NY (US); Virginia Commonwealth University, Richmond, VA (US).

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1. Bode, F. et al. *Stretch-induced vulnerability to atrial fibrillation is counteracted by Grammostola spatulata toxin*. Circulation 1999, 100(18, Suppl.): Abst 1784.

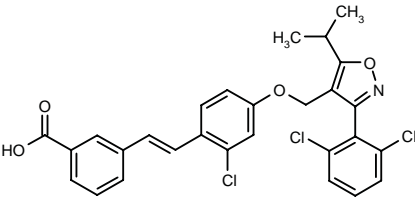
2. Suchyna, T.M. et al. *Identification of a peptide toxin from Grammostola spatulata spider venom that blocks cation-selective stretch-activated channels*. J Gen Physiol 2000, 115(5): 583.

GW-4064X

292539

3-[2-[2-Chloro-4-[3-(2,6-dichlorophenyl)-5-isopropyl-isoxazol-4-ylmethoxy]phenyl]vinyl]benzoic acid

GW-4064



C28 H22 Cl3 N O4; Mol wt: 542.8438

ACTION – Nonsteroidal ligand for the nuclear bile acid farnesoid X receptor (FXR, NR1H4; EC₅₀ = 70 nM) with partial agonist activity (EC₅₀ = 4.1 nM). Potentially useful as a tool for studying the role of this receptor in mammalian physiology and pathology.

SOURCE – Glaxo Wellcome.

REFERENCES

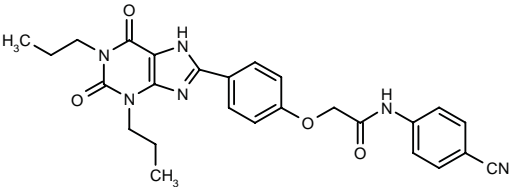
1. Blanchard, S.G. et al. (Glaxo Group Ltd.) *Assays for ligands for nuclear receptors*. WO 0037077.

2. Maloney, P.R. et al. *Identification of a non-steroidal ligand for the nuclear bile acid receptor FXR*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 316.

MRS-1754¹⁻⁴

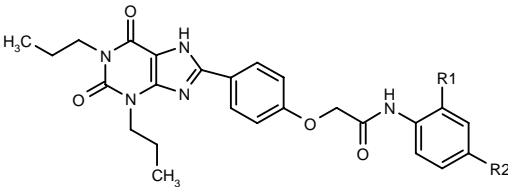
290922

N-(4-Cyanophenyl)-2-[4-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1H-purin-8-yl)phenoxy]acetamide



C26 H26 N6 O4; Mol wt: 486.5294

ACTION – Adenosine A_{2B} receptor antagonist with high binding affinity for human A_{2B} receptors over human A₁, A_{2A} and A₃ receptors (K_i = 1.97, 403, 503 and 570 nM, respectively). The antagonist activity at A_{2B} receptors was demonstrated in functional studies in HEK-293 cells stably expressing A_{2B} receptors, where compound (at 100 μM) completely inhibited NECA-induced calcium mobilization. Potentially useful as a pharmacological tool to elucidate the physiological role of the adenosine A_{2B} receptor subtype and, in tritiated form, as a selective radioligand for adenosine A_{2B} receptors. Other related compounds include the following:



Compound	R1	R2	Formula
MRS-1706 [292812]	H	Ac	C ₂₇ H ₂₉ N ₅ O ₅
MRS-1668 [292813]	Ac	H	C ₂₇ H ₂₉ N ₅ O ₅

SOURCES – Adenosine Therapeutics; National Institutes of Health, Bethesda, MD (US); University of Virginia, Charlottesville, VA (US).

REFERENCES

1. Jacobson, K.A. *Probing P1 and P2 receptors using novel ligands and mutagenesis*. Drug Dev Res 2000, 50(1): Abst S06-04.

2. Kim, Y.-C. et al. *Anilide derivatives of an 8-phenylxanthine carboxylic congener (XCC) are highly potent and selective antagonists at human A2B adenosine receptors*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 128.

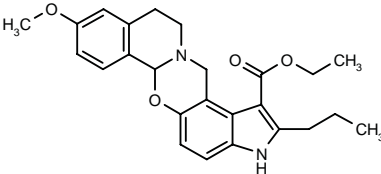
3. Kim, Y.-C. et al. *Anilide derivatives of an 8-phenylxanthine carboxylic congener are highly potent and selective antagonists at human A2B adenosine receptors*. J Med Chem 2000, 43(6): 1165.

4. *Adenosine Therapeutics enters license agreement for adenosine receptor antagonists*. DailyDrugNews.com (Daily Essentials) 2000, June 15.

PD-0298029

292458

9-Methoxy-2-propyl-3,11,12,14-tetrahydro-6aH-indolo[4',5':5,6][1,3]oxazino[2,3-a]isoquinoline-1-carboxylic acid ethyl ester



C25 H28 N2 O4; Mol wt: 420.5062

ACTION – Muscarinic M₄ receptor antagonist with high affinity and selectivity for M₄ over M₁, M₂ and M₃ receptors (IC₅₀ = 8, 4660, 2000 and 130 nM, respectively). Potentially useful as a pharmacological tool to elucidate the physiological role of this receptor.

SOURCE – Pfizer.

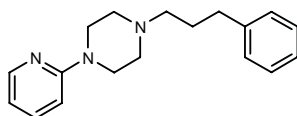
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1. Boehme, T.M. et al. *Benzoxazine isoquinoline as m4 selective muscarinic receptor antagonists*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 162.

PSC-38

292540

1-(3-Phenylpropyl)-4-(2-pyridyl)piperazine



C₁₈ H₂₃ N₃; Mol wt: 281.4007

ACTION – High-affinity σ_2 -receptor ligand (K_i = 6-25 nM), a potential lead structure for recognition at this site.

SOURCES – University of Maryland, Baltimore, MD (US); National Institutes of Health, Bethesda, MD (US).

REFERENCES

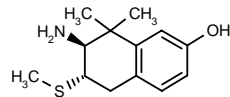
1. Maeda, D.Y. et al. *N-Arylalkylpiperidines: High affinity sigma-1 and sigma-2 receptor ligands*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MEDI 213.

**ANALGESIC AND ANESTHETIC
DRUGS**

ANALGESIC DRUGS

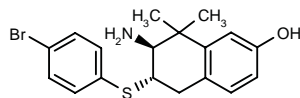
291759

(+)-*trans*-7-Amino-8,8-dimethyl-6-(methylsulfanyl)-5,6,7,8-tetrahydronaphthalen-2-ol



C13 H19 N O S; Mol wt: 237.3651

ACTION – Analgesic agent, an opioid receptor agonist with potential for the treatment of pain including chronic and acute pain. Another specifically claimed thio-aminotetralin is:



291761: C18 H20 Br N O S

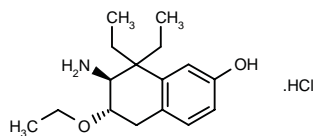
SOURCE – AstraZeneca.

REFERENCES

1. Dixit, D. et al. (Astra Pharma, Inc.; Astra AB) *Novel thio-aminotetralin cpds. useful in pain management.* WO 0037438.

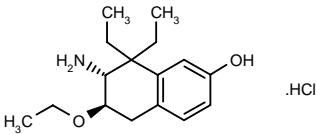
291762

(-)-*trans*-7-Amino-8,8-diethyl-6-ethoxy-5,6,7,8-tetrahydronaphthalen-2-ol hydrochloride



C16 H25 N O2 . HCl; Mol wt: 299.8394

ACTION – Analgesic agent, an opioid receptor agonist with potential for the treatment of pain including chronic and acute pain. Another specifically claimed oxo-aminotetralin is:



291763: C16 H25 N O2 . HCl: (+)-enantiomer

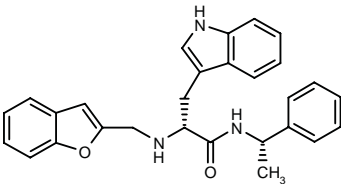
SOURCE – AstraZeneca.

REFERENCES

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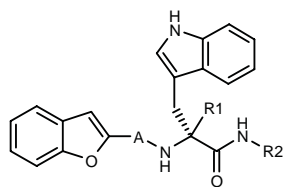
291888

2(*R*)-(2-Benzofurylmethylamino)-3-(1*H*-indol-3-yl)-*N*-[1(*S*)-phenylethyl]propionamide



C28 H27 N3 O2; Mol wt: 437.5403

ACTION – Highly selective and competitive, nonpeptide neurokinin NK₁ receptor antagonist displaying an IC₅₀ of 0.7 nM in an NK₁ binding assay using [¹²⁵I]-substance P as the ligand. Potentially useful in the treatment of CNS disorders such as pain, anxiety, depression, schizophrenia, neuralgia, stress, sexual dysfunction, bipolar, movement and cognitive disorders, obesity and addiction, allergic or inflammatory disorders such as arthritis, asthma, bronchitis, psoriasis, eczema, rhinitis, colitis and Crohn's disease, and neuropathological disorders such as scleroderma and emesis. Other specifically claimed compounds are:



Compound	R1	R2	A	Formula
291889	H	(S)-CH(Me)Ph	-(CH2)2-	C ₂₉ H ₂₉ N ₃ O ₂
291890	Me	(S)-CH(Me)Ph	-CH2NHCO-	C ₃₀ H ₃₀ N ₄ O ₃
291891	Me	4-Me-PhCH(Me)	-CH2-	C ₃₀ H ₃₁ N ₃ O ₂
291892	H	4-Me-PhCH(Me)	-CH2-	C ₂₉ H ₂₉ N ₃ O ₂
291893	H	4-F-PhCH(Me)	-CH2-	C ₂₈ H ₂₆ FN ₃ O ₂
291894	H	cyclohexyl-CH(Me)	-CH2-	C ₂₈ H ₃₃ N ₃ O ₂
291895	H	4-NO2-PhCH(Me)	-CH2-	C ₂₈ H ₂₆ N ₄ O ₄

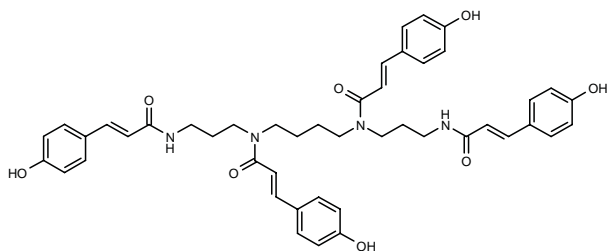
SOURCE – Pfizer.

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1. Creswell, M.W. et al. (Pfizer Inc.) *Non-peptide NK1 receptor antagonists*. WO 0037462.

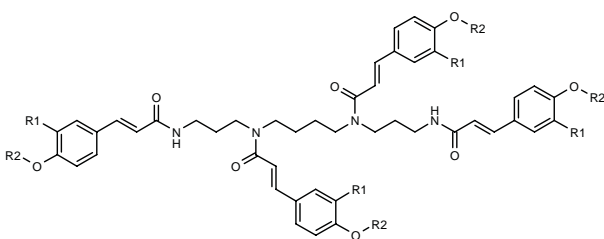
291965

1,20-Bis(4-hydroxyphenyl)-8,13-bis[3-(4-hydroxyphenyl)-2(*E*)-propenoyl]-4,8,13,17-tetrazaicosa-1(*E*),19(*E*)-diene-3,18-dione



C46 H50 N4 O8; Mol wt: 786.9210

ACTION – Tachykinin antagonist isolated from the plant *Matricaria chamomilla*, with an IC₅₀ value of 0.011 μM for inhibition of substance P-induced contractions in isolated guinea pig ileum. Potentially useful for tachykinin-related disorders such as inflammatory and allergic diseases, pain, anxiety, depression, schizophrenia and vomiting, among others. The invention also includes synthetic derivatives of the isolated compounds such as the following:



Compound	R1	R2	Formula
291966	H	Ac	C ₅₄ H ₅₈ N ₄ O ₁₂
291967	OMe	Ac	C ₅₈ H ₆₆ N ₄ O ₁₆
291968	OMe	H	C ₅₀ H ₅₈ N ₄ O ₁₂

SOURCE – Nippon Zoki.

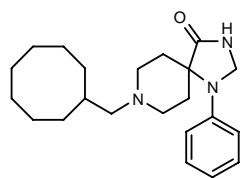
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1. Yamamoto, A. et al. (Nippon Zoki Pharmaceutical Co., Ltd.) *Substd. alkyltetramine derivs*. EP 1018506, JP 2000256293.

292060

8-Cyclooctylmethyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one

1'-(Cyclooctylmethyl)-3-phenylspiro[imidazolidine-4,4'-piperidin]-5-one



C22 H33 N3 O; Mol wt: 355.5227

ACTION – A representative compound from a series of heterocyclic compounds with potent affinity for the nociceptin ORL1 (N/OFQ) receptor (IC₅₀ = 41 nM). Potentially useful as an analgesic, as an alternative to narcotic analgesics in cases of resistance or dependence, as an antiobesity agent, for improving cerebral function and enhancing cognition, as a treatment for diabetes insipidus, polyuria and hypotension, and for CNS disorders such as schizophrenia, depression and Parkinson's disease.

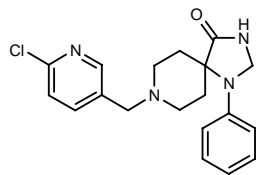
SOURCE – Banyu.

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1. Kawamoto, H. et al. (Banyu Pharmaceutical Co., Ltd.) *4-Oxoimidazolidine-5-spiro-nitrogen-containing heterocyclic cpds*. JP 2000169476.

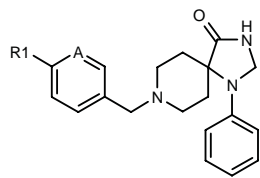
292158

8-(6-Chloropyridin-3-ylmethyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one



C19 H21 Cl N4 O; Mol wt: 356.8549

ACTION – Analgesic agent that displays both mu opioid receptor (MOP)-agonist activity (K_i = 0.4 nM) and dopamine D2 receptor-antagonist activity (K_i = 3.6 nM), and exerts potent analgesic effects in the hot-plate test in mice (ED₅₀ = 1.79 mg/kg i.p. vs. ED₅₀ = 13.72 mg/kg i.p. for morphine) with reduced side effects and dependence liability. Antidopamine activity was demonstrated by inhibition of apomorphine-induced climbing behavior in mice. Other exemplified compounds are:



Compound	R1	A	Formula
292159	OMe	CH	C ₂₁ H ₂₅ N ₃ O ₂
292160	Me	N	C ₂₀ H ₂₄ N ₄ O
292161	Br	CH	C ₂₀ H ₂₂ BrN ₃ O
292162	Me	CH	C ₂₁ H ₂₅ N ₃ O

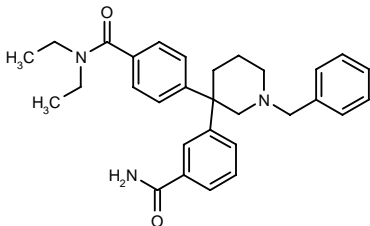
SOURCE – Meiji Seika.

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1. Akiyama, Y. et al. (Meiji Seika Kaisha, Ltd.) *Remedies for pain*. WO 0038720.

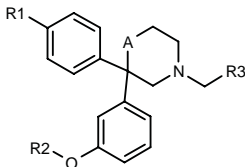
292281

4-[1-Benzyl-3-[3-(carbamoyl)phenyl]piperidin-3-yl]-N,N-diethylbenzamide



C30 H35 N3 O2; Mol wt: 469.6255

ACTION – Delta opioid receptor (DOP) ligand, potentially useful for the treatment of conditions affected by the modulation of opioid receptors such as chronic and neurogenic pain, organ and skin graft rejection, stroke, shock, Hodgkin’s disease, Sjögren’s disease, systemic lupus erythematosus, gastritis, irritable bowel syndrome and inflammatory diseases such as arthritis, psoriasis, asthma and inflammatory bowel disease. Other compounds from this series of 3,3-biaryl piperidine and 2,2-biaryl morpholine derivatives are:



Compound	R1	R2	R3	A	Formula
292282	C(Et)2OH	Me	vinyl	CH2	C ₂₆ H ₃₅ NO ₂
292283	CON(Et)2	H	cyclopropyl	O	C ₂₅ H ₃₂ N ₂ O ₃

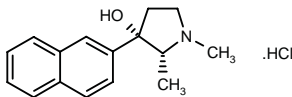
SOURCE – Pfizer.

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292864

(2*RS*,3*SR*)-1,2-Dimethyl-3-(2-naphthyl)pyrrolidin-3-ol hydrochloride



C16 H19 N O . HCl; Mol wt: 277.7930

ACTION – Analgesic agent proven to be 6-fold more potent than morphine in the hot-plate test in mice (AD₅₀ = 0.65 and 5.38 mg/kg i.p., respectively). The analgesic activity of compound appears to be mediated by activation of the opioid system, in particular delta opioid (DOP) receptors, as its effect was completely inhibited by the DOP antagonist naltrindole. It showed significantly less nonspecific muscle relaxant and sedative effects compared to morphine in the rotarod test in mice.

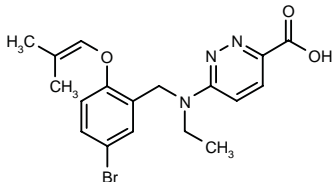
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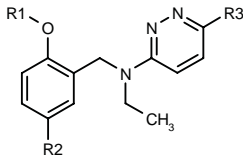
292904

6-[N-[5-Bromo-2-(2-methyl-1-propenyloxy)benzyl]-N-ethylamino]pyridazine-3-carboxylic acid



C18 H20 Br N3 O3; Mol wt: 406.2780

ACTION – Analgesic agent that antagonizes E₂-type prostaglandin effects and is expected to be of use for the treatment of mild to moderate pain. Other specifically claimed aromatic amine compounds include the following:



Compound	R1	R2	R3	Formula
292905	CH=C(Me)2	Br	5-tetrazolyl	C ₁₈ H ₂₀ BrN ₇ O
292906	CH=C(Cl)Me	Br	CONHSO2Pr	C ₂₀ H ₂₄ BrClN ₄ O ₄ S
292907	CH=C(Cl)Me	Br	CO2H	C ₁₇ H ₁₇ BrClN ₃ O ₃
292908	CH=C(Me)2	Cl	CO2H	C ₁₈ H ₂₀ ClN ₃ O ₃
292909	3-cyclohexenyl	Cl	3,5-(Me)2-4-isoxazolyl-SO2NHCO	C ₂₅ H ₂₈ ClN ₅ O ₅ S
292910	CH=C(Me)2	Cl	-CO-D,L-Ala-OH	C ₂₁ H ₂₅ ClN ₄ O ₄
292911	CH=C(Me)2	Br	4-Me-5-thiazolyl-SO2NHCO	C ₂₂ H ₂₄ BrN ₅ O ₄ S ₂

SOURCE – AstraZeneca.

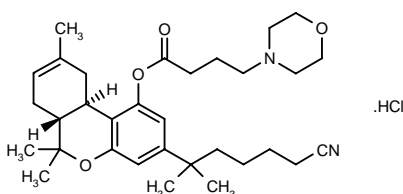
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1. Breault, G.A. (Zeneca, Ltd.) *Aromatic amine cpds. that antagonize the pain enhancing effects of prostaglandins*. US 6100258, WO 9700864.

O-1057

290475

4-Morpholinebutanoic acid (6a*R*,10a*R*)-3-(5-cyano-1,1-dimethylpentyl)-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]-1-benzopyran-1-yl ester hydrochloride



C32 H46 N2 O4 . HCl; Mol wt: 559.1863

ACTION – Nonopioid analgesic, a potent, water-soluble cannabinoid CB₁ and CB₂ receptor ligand (pK_i = 8.63 and 7.96, respectively) with *in vitro* functional agonist properties at both receptors (pEC₅₀ = 8.80 and 7.78, respectively, for inhibition of forskolin-stimulated cAMP production in CHO cells transfected with CB₁ and CB₂ receptors). In isolated mouse vas deferens, compound exhibited CB₁ receptor-agonist activity, as demonstrated by inhibition of electrically evoked contractions (pEC₅₀ = 9.73), and this effect was antagonized by the selective, competitive CB₁ receptor antagonist SR-141716A. *In vivo* experiments in mice demonstrated the ability of compound to activate CB₁ receptors; it reduced spontaneous motility (ED₅₀ = 0.02 and 16.4 mg/kg i.v. and p.o., respectively), lowered rectal temperature (ED₅₀ = 0.06 and 6.8 mg/kg i.v. and p.o., respectively) and exhibited antinociceptive activity in the tail-flick test (ED₅₀ = 0.02 and 6.3 mg/kg i.v. and p.o., respectively). Compound also showed antinociceptive activity when nebulized at a concentration of 1 mg/ml for 10 min in mice. Potentially useful for the relief of chronic pain.

SOURCES – Organix; Virginia Commonwealth University, Richmond, VA (US).

REFERENCES

1. Martin, B.R. and Razdan, R.K. (Virginia Commonwealth University) *Water soluble derivs. of cannabinoids*. US 5847128.

2. Gibson, T.M. et al. 3-(5-Cyano-1',1'-dimethylpentyl)-1-(4-*N*-morpholinobutyryloxy)- Δ^8 -THC hydrochloride, a potent water-soluble cannabinoid receptor agonist with antinociceptive properties. Symp Cannabinoids (June 22-24, Hunt Valley) 2000, 34.

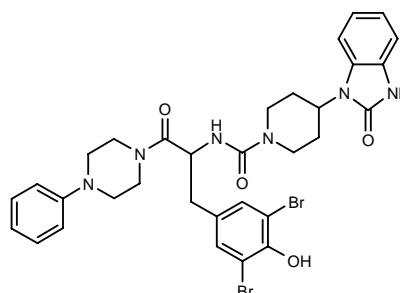
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4. Pertwee, R.G. et al. O-1057, a potent water-soluble cannabinoid receptor agonist with antinociceptive properties. Br J Pharmacol 2000, 129(8): 1577.

ANTIMIGRAINE DRUGS

293084

N-[1-(3,5-Dibromo-4-hydroxybenzyl)-2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1-carboxamide



C32 H34 Br2 N6 O4; Mol wt: 726.4666

ACTION – Nonpeptide calcitonin gene-related peptide (CGRP) antagonist with a pK_i value of 7.8 for displacement of radiolabeled CGRP binding in human neuroblastoma SK-N-MC cell membranes and a pA₂ value of 7.7 for inhibition of CGRP-induced cAMP production in SK-N-MC cells. Compound was also found to antagonize the CGRP-induced relaxation of isolated human, but not guinea pig, cerebral arteries. Potentially useful for the treatment of migraine.

SOURCES – Boehringer Ingelheim; Merck & Co.

REFERENCES

1. Rudolf, K. et al. (Dr. Karl Thomae GmbH) *Modified aminoacids, pharmaceuticals containing these cpds. and methods for their production*. JP 2000505100, WO 9811128.

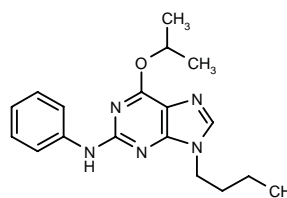
2. Edvinsson, L. et al. *Characterization of the effects of a nonpeptide CGRP receptor antagonist in SK-N-MC cells and isolated human cerebral arteries*. Cephalalgia 2000, 20(4): Abst 17.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

291996

N-(9-Butyl-6-isopropoxy-9*H*-purin-2-yl)-*N*-phenylamine



C18 H23 N5 O; Mol wt: 325.4137

SOURCE – AstraZeneca.

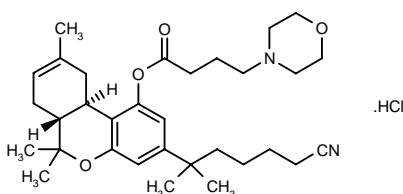
REFERENCES

1. Breault, G.A. (Zeneca, Ltd.) *Aromatic amine cpds. that antagonize the pain enhancing effects of prostaglandins*. US 6100258, WO 9700864.

O-1057

290475

4-Morpholinebutanoic acid (6a*R*,10a*R*)-3-(5-cyano-1,1-dimethylpentyl)-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]-1-benzopyran-1-yl ester hydrochloride



C32 H46 N2 O4 . HCl; Mol wt: 559.1863

ACTION – Nonopioid analgesic, a potent, water-soluble cannabinoid CB₁ and CB₂ receptor ligand (pK_i = 8.63 and 7.96, respectively) with *in vitro* functional agonist properties at both receptors (pEC₅₀ = 8.80 and 7.78, respectively, for inhibition of forskolin-stimulated cAMP production in CHO cells transfected with CB₁ and CB₂ receptors). In isolated mouse vas deferens, compound exhibited CB₁ receptor-agonist activity, as demonstrated by inhibition of electrically evoked contractions (pEC₅₀ = 9.73), and this effect was antagonized by the selective, competitive CB₁ receptor antagonist SR-141716A. *In vivo* experiments in mice demonstrated the ability of compound to activate CB₁ receptors; it reduced spontaneous motility (ED₅₀ = 0.02 and 16.4 mg/kg i.v. and p.o., respectively), lowered rectal temperature (ED₅₀ = 0.06 and 6.8 mg/kg i.v. and p.o., respectively) and exhibited antinociceptive activity in the tail-flick test (ED₅₀ = 0.02 and 6.3 mg/kg i.v. and p.o., respectively). Compound also showed antinociceptive activity when nebulized at a concentration of 1 mg/ml for 10 min in mice. Potentially useful for the relief of chronic pain.

SOURCES – Organix; Virginia Commonwealth University, Richmond, VA (US).

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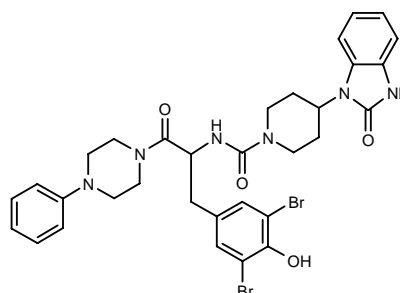
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ANTIMIGRAINE DRUGS

293084

N-[1-(3,5-Dibromo-4-hydroxybenzyl)-2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1-carboxamide



C32 H34 Br2 N6 O4; Mol wt: 726.4666

ACTION – Nonpeptide calcitonin gene-related peptide (CGRP) antagonist with a pK_i value of 7.8 for displacement of radiolabeled CGRP binding in human neuroblastoma SK-N-MC cell membranes and a pA₂ value of 7.7 for inhibition of CGRP-induced cAMP production in SK-N-MC cells. Compound was also found to antagonize the CGRP-induced relaxation of isolated human, but not guinea pig, cerebral arteries. Potentially useful for the treatment of migraine.

SOURCES – Boehringer Ingelheim; Merck & Co.

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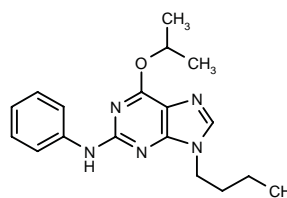
2. Edvinsson, L. et al. *Characterization of the effects of a nonpeptide CGRP receptor antagonist in SK-N-MC cells and isolated human cerebral arteries*. Cephalalgia 2000, 20(4): Abstr 17.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

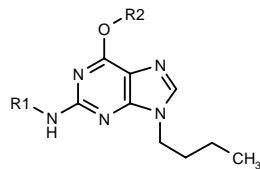
291996

N-(9-Butyl-6-isopropoxy-9*H*-purin-2-yl)-*N*-phenylamine



C18 H23 N5 O; Mol wt: 325.4137

ACTION – Brain GABA_A receptor ligand that acts at the benzodiazepine binding site of the GABA_A receptor, potentially useful in the treatment of CNS disorders such as anxiety, depression, insomnia and dementia, as well as for detecting the location of GABA_A receptors in tissue samples via autoradiography or positron emission tomography. Other specifically claimed 2-amino-9-alkylpurines include the following:



Compound	R1	R2	Formula
291997	Ph	2-Pyr-CH2	C ₂₁ H ₂₂ N ₆ O
291998	4-F-Ph	Me	C ₁₆ H ₁₈ FN ₅ O
291999	4-MeO-Ph	Me	C ₁₇ H ₂₁ N ₅ O ₂
292000	2,4-(Me)2-Ph	Et	C ₁₉ H ₂₅ N ₆ O
292001	6-MeO-3-Pyr	2-THF-CO	C ₂₀ H ₂₄ N ₆ O ₄
292002	6-EtO-3-Pyr	CH2CH2OMe	C ₁₉ H ₂₆ N ₆ O ₃
292003	6-EtO-3-Pyr	CH2CO2Et	C ₂₀ H ₂₆ N ₆ O ₄
292004	3-quinolyl	CH2CH2F	C ₂₀ H ₂₁ FN ₆ O

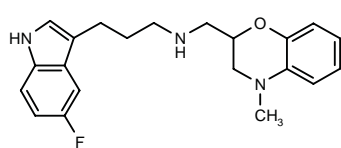
SOURCE – Neurogen.

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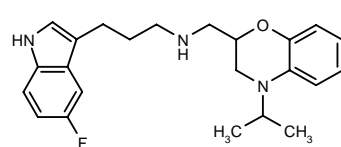
292345

N-[3-(5-Fluoro-1 *H*-indol-3-yl)propyl]-*N*-(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylmethyl)amine



C21 H24 F N3 O; Mol wt: 353.4386

ACTION – Dual-action compound that interacts with the 5-HT_{1A} receptor and inhibits 5-HT reuptake and is therefore expected to be useful for the treatment of anxiety and depression. Another exemplified compound is:



292346: C23 H28 F N3 O

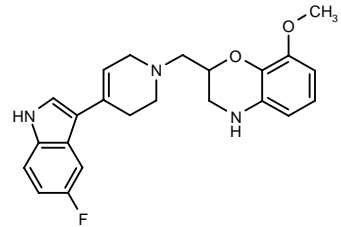
SOURCE – American Home Products.

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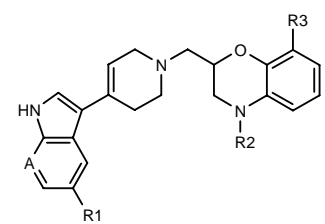
292347

2-[4-(5-Fluoro-1 *H*-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-ylmethyl]-8-methoxy-3,4-dihydro-2*H*-1,4-benzoxazine



C23 H24 F N3 O2; Mol wt: 393.4596

ACTION – Dual-action compound that interacts with 5-HT_{1A} receptors and inhibits 5-HT reuptake and is therefore expected to be useful for the treatment of anxiety and depression. Other exemplified 3,4-dihydro-2*H*-benzo[1,4]oxazine derivatives are:



Compound	R1	R2	R3	A	Formula
292348	F	Me	OMe	CH	C ₂₄ H ₂₆ FN ₃ O ₂
292349	F	Et	OMe	CH	C ₂₅ H ₂₈ FN ₃ O ₂
292350	F	Pr	OMe	CH	C ₂₆ H ₃₀ FN ₃ O ₂
292351	H	H	H	CH	C ₂₂ H ₂₃ N ₃ O
292352	H	Ph	H	N	C ₂₇ H ₂₆ N ₄ O
292353	F	4-CF3-Ph	OMe	CH	C ₃₀ H ₂₇ F ₄ N ₃ O ₂

SOURCE – American Home Products.

REFERENCES

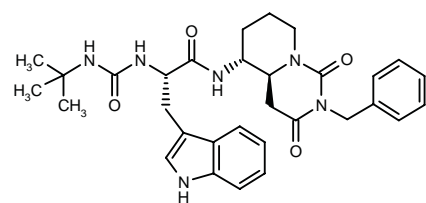
1. Mewshaw, R.E. and Shah, U.S. (American Home Products Corp.) 3,4-Dihydro-2*H*-benzo[1,4]oxazine derivs. WO 0040581.

IQM-97423

282194

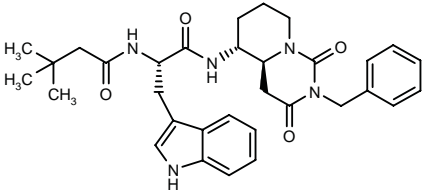
N-[(4*aS*,5*R*)-2-Benzyl-1,3-dioxoperhydropyrido[1,2-*c*]-pyrimidin-5-yl]-2-(*S*)-(3-*tert*-butylureido)-3-(1*H*-indol-3-yl)propionamide

*N*¹-[(4*aS*,5*R*)-2-Benzyl-1,3-dioxoperhydropyrido[1,2-*c*]-pyrimidin-5-yl]-*N*²-(*N*-*tert*-butylcarbamoyl)-*L*-tryptophanamide



C31 H38 N6 O4; Mol wt: 558.6792

ACTION – Cholecystokinin CCK₁ receptor antagonist with high affinity and selectivity for CCK₁ receptors over CCK₂ receptors (IC₅₀ = 0.91 and > 10,000 nM, respectively). *In vivo*, compound strongly reduced, both after i.p. and p.o. administration, the increase in plasma amylase levels induced by caerulein injections in a model of pancreatitis in rats, and it antagonized hypomotility induced by CCK-8 in mice. When given at doses of 0.01-1 mg/kg i.p., it exhibited anxiolytic-like effects similar to the CCK₁ receptor antagonist devazepide and to the CCK₂ receptor antagonist PD-135158 in the light/dark box test in mice, whereas it was more active than devazepide in the plus-maze test in rats; it was also active when given by the oral route. Potentially useful as an anxiolytic agent. Another related compound is:



IQM-97422 [282193]: C32 H39 N5 O4

SOURCES – CSIC, Madrid (ES); Universidad de Navarra, Pamplona (ES).

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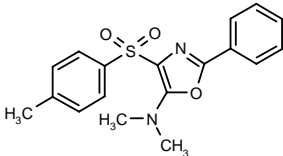
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ANTIPSYCHOTIC DRUGS

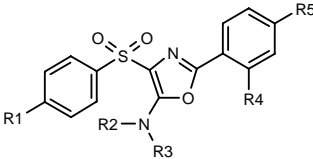
291871

N,N-Dimethyl-*N*-[4-(4-methylphenylsulfonyl)-2-phenyloxazol-5-yl]amine



C18 H18 N2 O3 S; Mol wt: 342.4172

ACTION – Agent with selective binding affinity for the 5-HT₆ receptor, useful for the treatment of CNS disorders such as psychosis, schizophrenia, depression, neurological diseases, cognition disorders, Parkinson’s disease, eating disorders, etc. Other specifically claimed sulfonyloxazolamines are:



Compound	R1	R2	R3	R4	R5	Formula
291872	Me	Me	Me	Cl	Cl	C ₁₈ H ₁₆ Cl ₂ N ₂ O ₃ S
291873	Cl	H	CH2Ph	Cl	H	C ₂₂ H ₁₆ Cl ₂ N ₂ O ₃ S
291874	H	H	Me	Me	H	C ₁₇ H ₁₆ N ₂ O ₃ S
291875	Me	H	CH2Ph	Cl	Cl	C ₂₃ H ₁₈ Cl ₂ N ₂ O ₃ S
291876	H	H	CH2Ph	Cl	Cl	C ₂₂ H ₁₆ Cl ₂ N ₂ O ₃ S
291877	H	Me	Me	Cl	Cl	C ₁₇ H ₁₄ Cl ₂ N ₂ O ₃ S

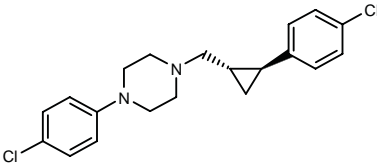
SOURCE – Merck KGaA.

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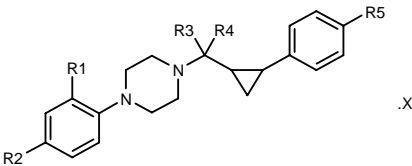
292382¹

trans-1-(4-Chlorophenyl)-4-[2-(4-chlorophenyl)cyclopropylmethyl]piperazine



C20 H22 Cl2 N2; Mol wt: 361.3138

ACTION – Dopamine receptor ligand with high affinity and selectivity for the dopamine D4 subtype (K_i = 8 and 523 nM for D4 and D2 subtypes, respectively), potentially useful for the treatment of psychotic disorders such as schizophrenia, as well as other dopamine-mediated diseases including parkinsonism and tardive dyskinesia. Other exemplified compounds from this series of 1-phenyl-4-[1-(2-aryl)cyclopropyl]methylpiperazines are:



Compound	R1	R2	R3	R4	R5	X	Isomer	Formula
292383 ¹	H	Cl	-O-	Cl			trans	C ₂₀ H ₂₀ Cl ₂ N ₂ O
292384 ¹⁻³	Me	Me	H	H	H	HBr	1S,2S	C ₂₂ H ₂₈ N ₂ ·HBr
292385 ¹	Me	Me	H	H	H	HBr	1R,2R	C ₂₂ H ₂₈ N ₂ ·HBr

SOURCE – Neurogen.

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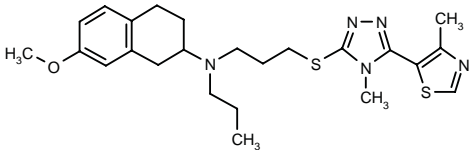
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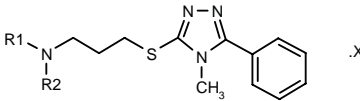
292455

N-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-[3-[4-methyl-5-(4-methylthiazol-5-yl)-4*H*-1,2,4-triazol-3-ylsulfanyl]propyl]-*N*-propylamine



C24 H33 N5 O S2; Mol wt: 471.6907

ACTION – Agent with selective affinity for dopamine D3 receptors, exhibiting a p*K*_i value of 8.06 for dopamine D3 receptors and a selectivity index (*K*_i D2/*K*_i D3) of 157. The compound is preferably useful for the treatment of schizophrenia and affective disorders. Other exemplified triazole compounds include the following:



Compound	R1	R2	X	Formula
292456	Pr	2-indanyl	fumarate	C ₂₄ H ₃₀ N ₄ S.C ₄ H ₄ O ₄
292457	H	6-Me-1,2,3,4-tetrahydro-2-Naph-CH2		C ₂₄ H ₃₀ N ₄ S

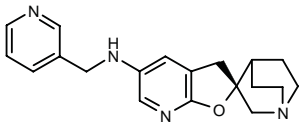
SOURCE – BASF.

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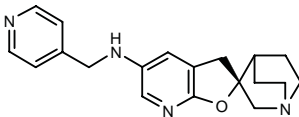
292513

(*R*)-(-)-*N*-[2,3-Dihydrospiro[furo[2,3-*b*]pyridine-2,3'-quinuclidin]-5-yl]-*N*-(3-pyridylmethyl)amine



C19 H22 N4 O; Mol wt: 322.4098

ACTION – Selective agonist at the α 7 nicotinic acetylcholine receptor subtype, particularly useful for the treatment of psychotic disorders such as schizophrenia, anxiety or mania and cognition disorders such as Alzheimer's disease. It may also be useful for the treatment of jet lag, nicotine addiction, pain, ulcerative colitis and neurodegenerative disorders in which there is a loss of cholinergic synapses, e.g., Parkinson's disease, Huntington's disease or Tourette's syndrome. Another specifically claimed spirofuropyridine is:



292514: C19 H22 N4 O

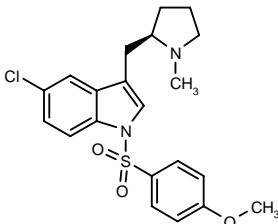
SOURCE – AstraZeneca.

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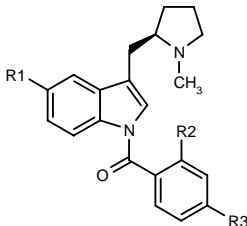
292996

5-Chloro-1-(4-methoxyphenylsulfonyl)-3-[1-methylpyrrolidin-2(*R*)-ylmethyl]-1*H*-indole



C21 H23 Cl N2 O3 S; Mol wt: 418.9427

ACTION – Agent for the treatment of schizophrenia, a 5-ht₆ receptor antagonist with high affinity for human 5-ht₆ receptors (*K*_i < 1 nM) and at least 100-fold selectivity relative to human 5-HT_{2C} and 5-HT₇ receptors. Its antagonist activity was demonstrated by inhibition of 5-HT-induced cAMP accumulation in transfected HEK293 cells (EC₅₀ = 8.4 nM). Other exemplified indole compounds are:



Compound	R1	R2	R3	Formula
292997	cyclohexyl-O	Cl	H	C ₂₇ H ₃₁ ClN ₂ O ₂
292998	Cl	H	F	C ₂₁ H ₂₀ ClFN ₂ O

SOURCE – NPS Allelix.

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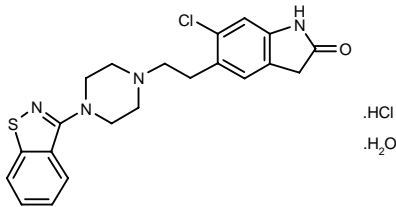
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ZIPRASIDONE HYDROCHLORIDE*
Rec INN; USAN

199378

5-[2-[4-(1,2-Benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloroindolin-2-one hydrochloride hydrate

CP-88059-01⁺



C21 H21 Cl N4 O S . HCl . H2O; Mol wt: 467.4186

ACTION – Antipsychotic agent with affinity for dopamine D2 and 5-HT₂ receptors.

INDICATION – Treatment of schizophrenia.

PRESENTATION – Capsules, equivalent to 20, 40, 60 and 80 mg ziprasidone; solution for i.m. injection, equivalent to 20 mg/ml ziprasidone.

PROPRIETARY NAME – Zeldox (SE).

SOURCE – Pfizer.

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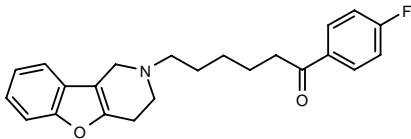
MONOGRAPH – Howard, H.R. et al. *Ziprasidone hydrochloride*. Drugs Fut 1994, 19(6): 0560.

⁺Drug Data Rep 1993, 015(11): 1000.

**TREATMENT OF MOOD
DISORDERS**

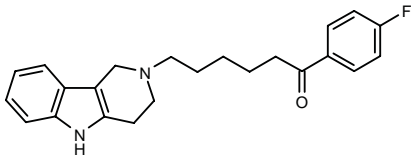
291827

1-(4-Fluorophenyl)-6-(1,2,3,4-tetrahydrobenzofuro-[3,2-c]pyridin-2-yl)hexan-1-one



C23 H24 F N O2; Mol wt: 365.4456

ACTION – Central α_2 -adrenoceptor antagonist for the treatment of depression and Parkinson's disease. The compound is selective for α_{2A} -adrenoceptors versus dopamine D2 receptors ($IC_{50} = 0.26$ nM and 0.40 μ M, respectively; selectivity ratio $D2/\alpha_{2A} = 1,950$), reducing the risk of extrapyramidal side effects. A representative compound from a series of benzisoxazoles and phenones wherein the following is also included:



291828: C23 H25 F N2 O

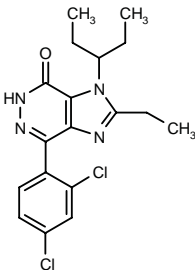
SOURCE – Janssen.

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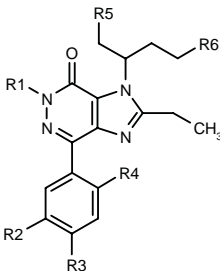
292293

4-(2,4-Dichlorophenyl)-2-ethyl-1-(1-ethylpropyl)-6,7-dihydro-1*H*-imidazo[4,5-*d*]pyridazin-7-one



C18 H20 Cl2 N4 O; Mol wt: 379.2890

ACTION – Corticotropin-releasing factor (CRF) antagonist, potentially useful in the treatment of depression, anxiety, posttraumatic stress disorder, eating disorders, irritable bowel syndrome, as well as immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychiatric disorders. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
292294	Me	H	Cl	Cl	Me	H	C ₁₉ H ₂₂ Cl ₂ N ₄ O
292295	Et	H	Cl	Cl	Me	H	C ₂₀ H ₂₄ Cl ₂ N ₄ O
292296	Pr	H	Cl	Cl	Me	H	C ₂₁ H ₂₆ Cl ₂ N ₄ O
292297	cyclopropyl-CH2	H	Cl	Cl	Me	H	C ₂₂ H ₂₆ Cl ₂ N ₄ O
292298	Me	H	CF3	CF3	Me	H	C ₂₁ H ₂₂ F ₆ N ₄ O
292299	Me	H	Cl	Cl	H	Me	C ₁₉ H ₂₂ Cl ₂ N ₄ O
292300	H	H	Cl	Cl	H	Me	C ₁₈ H ₂₀ Cl ₂ N ₄ O
292301	Me	Me	OMe	Me	H	Me	C ₂₂ H ₃₀ N ₄ O ₂

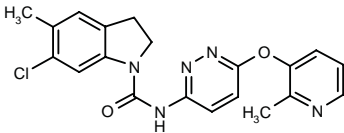
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Gilligan, P.J. and Bakthavatchalam, R. (DuPont Pharmaceuticals Co.) *1*H*-Imidazo[4,5-*d*]pyridazin-7-ones, 3*H*-imidazo[4,5-*c*]pyridin-4-ones and corresponding thiones as corticotropin releasing factor (CRF) receptor ligands*. WO 0039127.

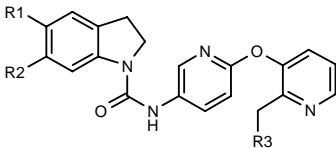
292968

6-Chloro-5-methyl-*N*-[6-(2-methylpyridin-3-yloxy)pyridazin-3-yl]indoline-1-carboxamide



C20 H18 Cl N5 O2; Mol wt: 395.8482

ACTION – High-affinity 5-HT_{2C} receptor ligand (pK_i = 8.7) with high selectivity over 5-HT_{2A} and 5-HT_{2B} receptors (pK_i = 5.8 and 6.8, respectively). In a human 5-HT_{2C} receptor functional assay, compound was found to be an inverse agonist. *In vivo*, it exhibited potent activity in reversing the hypolocomotion induced by mCPP in rats (ID₅₀ = 1.6 mg/kg p.o.). Potentially useful as a nonsedating anxiolytic and antidepressant.



Compound	R1	R2	R3	Formula
292965	CF3	H	H	C ₂₁ H ₁₇ F ₃ N ₄ O ₂
292967	Me	Cl	Me	C ₂₂ H ₂₁ ClN ₄ O ₂

SOURCE – SmithKline Beecham.

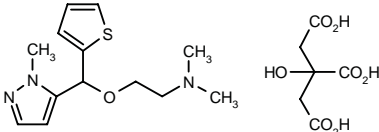
REFERENCES

1. Bromidge, S.M. et al. (SmithKline Beecham plc.) *Indoline derivs. useful as 5-HT_{2C} receptor antagonists*. EP 0912554, JP 2000512306, WO 9748699.
2. Bromidge, S.M. et al. *1-[2-(Heteroarylloxy)heteroaryl]carbamoylindolines: Novel and selective 5-HT_{2C} receptor inverse agonists with potential as antidepressant/anxiolytic agents*. Bioorg Med Chem Lett 2000, 10(16): 1863.

E-6006*

281886

N,N-Dimethyl-*N*-[2-[1-(1-methyl-1*H*-pyrazol-5-yl)-1-(2-thienyl)methoxy]ethyl]amine citrate



C13 H19 N3 O S . C6 H8 O7; Mol wt: 457.5013

ACTION – Antidepressant with moderate to low affinity for σ_1 ($K_i = 0.894 \mu\text{M}$), muscarinic M_1 , M_2 , M_3 and M_5 ($K_i = 1.39, 2.62, 1.5$ and $1.39 \mu\text{M}$, respectively), 5-HT_{2A} ($K_i = 1.79 \mu\text{M}$) and 5-HT_7 receptors ($K_i = 2.64 \mu\text{M}$), as well as for the 5-HT reuptake transporter ($K_i = 3.77 \mu\text{M}$). Compound was active in two animal models of depression: the tail-suspension test in mice ($\text{ED}_{50} = 31 \text{ mg/kg i.p.}$) and the forced swimming test in rats, where at a dose of 80 mg/kg it significantly reduced immobility time by 49 and 56% after i.p. and p.o. administration, respectively. In addition, compound antagonized ptosis induced by reserpine ($\text{ED}_{50} = 28 \text{ mg/kg p.o.}$) without affecting spontaneous locomotor activity in rats. Pharmacokinetic studies in rats and dogs indicated good oral bioavailability (32 and 69%, respectively), with rapid absorption ($t_{\text{max}} = 0.25$ and 0.8 h , respectively) and elimination ($t_{1/2} = 0.8$ and 4.5 h , respectively).

SOURCE – Esteve.

REFERENCES

1. Merce-Vidal, R. et al. (Laboratorios del Dr. Esteve, SA) *Thienylazolyalcoxyethanamines, their preparation and their application as medicaments*. WO 9952525.

2. Fisas, M.A. et al. *Pharmacological profile of E-6006 citrate, a novel potential antidepressant*. Methods Find Exp Clin Pharmacol 2000, 22(6): Abst P-75.

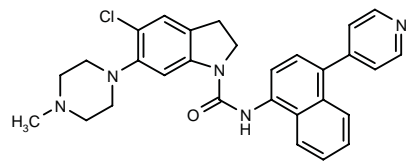
3. Puig, S. et al. *Pharmacokinetics of E-6006, a new antidepressant agent, in rats and dogs*. Methods Find Exp Clin Pharmacol 2000, 22(6): Abst P-72.

*Identified compound **281886** (see **281884**) Drug Data Rep 1999, 021(11): 0953.

SB-272183*

271107

5-Chloro-6-(4-methylpiperazin-1-yl)-N-[4-(4-pyridyl)-naphthalen-1-yl]indoline-1-carboxamide



C29 H28 Cl N5 O; Mol wt: 498.0272

ACTION – Mixed $5\text{-HT}_{1A/1B/1D}$ receptor antagonist ($\text{pK}_i = 8.3, 8.3$ and 8.9 for binding affinity at 5-HT_{1A} , 5-HT_{1B} and 5-HT_{1D} receptors, respectively) with high selectivity against other serotonin subtype receptors ($\text{pK}_i < 6.8$), dopamine D2 and D3 receptors $\text{pK}_i = 5.3$ and 5.5 , respectively) and α_1 -adrenoceptors ($\text{pK}_i = 5.7$). Compound has no effect on cell firing in rat dorsal raphe nuclei but was able to reverse 8-OH-DPAT -induced inhibition of cell firing, indicating an antagonism of presynaptic 5-HT_{1A} receptors. In addition, the ability of compound to increase the release of 5-HT in rat cortical slices demonstrated antagonism at presynaptic 5-HT_{1B} receptors. Potentially useful as an antidepressant.

SOURCE – SmithKline Beecham.

REFERENCES

1. Gaster, L.M. et al. (SmithKline Beecham plc) *Indole derivs. having combined 5HT_{1A} , 5HT_{1B} and 5HT_{1D} receptor antagonist activity*. EP 0975593, WO 9850358.

2. Evans, M. et al. *Mixed $5\text{-HT}_{1A/1B/1D}$ receptor antagonists as novel antidepressants*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-77.

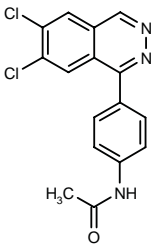
*Identified compound **271107** (see **271106**) Drug Data Rep 1999, 021(02): 0116.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

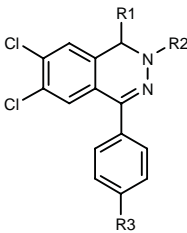
292326

N-[4-(6,7-Dichlorophthalazin-1-yl)phenyl]acetamide



C16 H11 Cl2 N3 O; Mol wt: 332.1889

ACTION – Phthalazine derivative that acts as a positive or negative allosteric modulator of the AMPA/kainate receptor and may be useful as an anticonvulsant, neuro-protectant, memory enhancer and muscle relaxant. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
292327	Me	H	NHAc	C ₁₇ H ₁₆ Cl ₂ N ₃ O
292328	Me	CO2Ph	NHAc	C ₂₄ H ₁₉ Cl ₂ N ₃ O ₃
292329	Me	CONHBu	NHAc	C ₂₂ H ₂₄ Cl ₂ N ₄ O ₂
292330	Me	CONHBu	NH2	C ₂₀ H ₂₂ Cl ₂ N ₄ O
292331	bond		NO2	C ₁₄ H ₇ Cl ₂ N ₃ O ₂
292332	H	H	NO2	C ₁₄ H ₉ Cl ₂ N ₃ O ₂
292333	H	Ac	NO2	C ₁₆ H ₁₁ Cl ₂ N ₃ O ₃
292334	H	Ac	NH2	C ₁₆ H ₁₃ Cl ₂ N ₃ O
292335	H	CONHBu	NH2	C ₁₉ H ₂₀ Cl ₂ N ₄ O
292336	bond		NH2	C ₁₄ H ₉ Cl ₂ N ₃

SOURCE – Egis.

REFERENCES

1. Lukács, G. et al. (Egis Pharmaceuticals Ltd.) *Phthalazine derivs., a process for the preparation thereof, and a pharmaceutical compsn. containing the same*. WO 0039100.

ACTION – Antidepressant with moderate to low affinity for σ_1 ($K_i = 0.894 \mu\text{M}$), muscarinic M_1 , M_2 , M_3 and M_5 ($K_i = 1.39, 2.62, 1.5$ and $1.39 \mu\text{M}$, respectively), 5-HT_{2A} ($K_i = 1.79 \mu\text{M}$) and 5-HT_7 receptors ($K_i = 2.64 \mu\text{M}$), as well as for the 5-HT reuptake transporter ($K_i = 3.77 \mu\text{M}$). Compound was active in two animal models of depression: the tail-suspension test in mice ($\text{ED}_{50} = 31 \text{ mg/kg i.p.}$) and the forced swimming test in rats, where at a dose of 80 mg/kg it significantly reduced immobility time by 49 and 56% after i.p. and p.o. administration, respectively. In addition, compound antagonized ptosis induced by reserpine ($\text{ED}_{50} = 28 \text{ mg/kg p.o.}$) without affecting spontaneous locomotor activity in rats. Pharmacokinetic studies in rats and dogs indicated good oral bioavailability (32 and 69%, respectively), with rapid absorption ($t_{\text{max}} = 0.25$ and 0.8 h , respectively) and elimination ($t_{1/2} = 0.8$ and 4.5 h , respectively).

SOURCE – Esteve.

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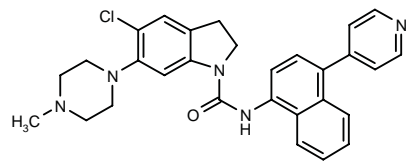
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*Identified compound **281886** (see **281884**) Drug Data Rep 1999, 021(11): 0953.

SB-272183*

271107

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C29 H28 Cl N5 O; Mol wt: 498.0272

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SOURCE – SmithKline Beecham.

REFERENCES

1. Gaster, L.M. et al. (SmithKline Beecham plc) *Indole derivs. having combined 5HT_{1A} , 5HT_{1B} and 5HT_{1D} receptor antagonist activity*. EP 0975593, WO 9850358.

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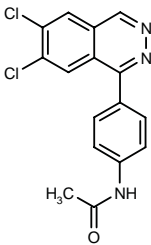
*Identified compound **271107** (see **271106**) Drug Data Rep 1999, 021(02): 0116.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

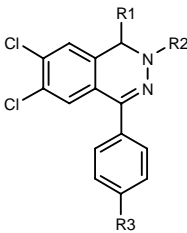
292326

N-[4-(6,7-Dichlorophthalazin-1-yl)phenyl]acetamide



C16 H11 Cl2 N3 O; Mol wt: 332.1889

ACTION – Phthalazine derivative that acts as a positive or negative allosteric modulator of the AMPA/kainate receptor and may be useful as an anticonvulsant, neuro-protectant, memory enhancer and muscle relaxant. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
292327	Me	H	NHAc	C ₁₇ H ₁₅ Cl ₂ N ₃ O
292328	Me	CO2Ph	NHAc	C ₂₄ H ₁₉ Cl ₂ N ₃ O ₃
292329	Me	CONHBu	NHAc	C ₂₂ H ₂₄ Cl ₂ N ₄ O ₂
292330	Me	CONHBu	NH2	C ₂₀ H ₂₂ Cl ₂ N ₄ O
292331	bond		NO2	C ₁₄ H ₇ Cl ₂ N ₃ O ₂
292332	H	H	NO2	C ₁₄ H ₉ Cl ₂ N ₃ O ₂
292333	H	Ac	NO2	C ₁₆ H ₁₁ Cl ₂ N ₃ O ₃
292334	H	Ac	NH2	C ₁₆ H ₁₃ Cl ₂ N ₃ O
292335	H	CONHBu	NH2	C ₁₉ H ₂₀ Cl ₂ N ₄ O
292336	bond		NH2	C ₁₄ H ₉ Cl ₂ N ₃

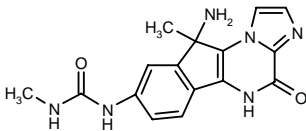
SOURCE – Egis.

REFERENCES

1. Lukács, G. et al. (Egis Pharmaceuticals Ltd.) *Phthalazine derivs., a process for the preparation thereof, and a pharmaceutical compsn. containing the same*. WO 0039100.

292879

(+)-*N*-(10-Amino-10-methyl-4-oxo-5,10-dihydro-4*H*-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-8-yl)-*N'*-methylurea



C16 H16 N6 O2; Mol wt: 324.3424

ACTION – Potent and selective glutamate AMPA receptor antagonist with nanomolar affinity for the AMPA receptor (IC_{50} = 10 nM) and 3,300-fold selectivity over the glycine site on the NMDA receptor complex (IC_{50} = 32 μ M). Its AMPA-antagonist activity was demonstrated *in vitro* by inhibition of currents generated by kainate in *Xenopus* oocytes (IC_{50} = 29.5 nM). Compound was able to protect against maximal electroshock (MES) seizures in mice (ED_{40} = 10, 2.5 and 4.6 mg/kg after i.v., i.p. and s.c. administration, respectively) and audiogenic seizures in DBA/2 mice (ED_{50} = 1.8 mg/kg i.p.). In the MES test, compound showed a long duration of action following i.v. administration (ED_{50} = 2.5, 5 and 10 mg/kg at 15, 30 and 60 min after dosing, respectively).

SOURCE – Aventis Pharma.

REFERENCES

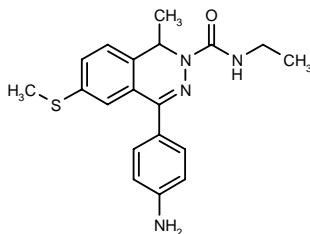
1. Aloup, J.-C. et al. (Rhône-Poulenc Rorer SA) *Imidazo (1,2-a)-indeno (1,2-e) pyrazin-4-one derivs. and pharmaceutical compsns. containing same.* US 5807859, WO 9526350.

2. Jimonet, P. et al. *8-Methylureido-10-amino-10-methyl-imidazo[1,2-a]indeno[1,2-e]-pyrazine-4-ones: Highly in vivo potent and selective AMPA receptor antagonists.* Bioorg Med Chem 2000, 8(8): 2211.

SYM-2259

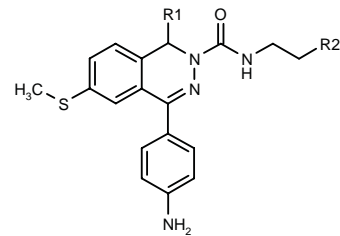
292542

4-(4-Aminophenyl)-*N*-ethyl-1-methyl-6-(methylsulfanyl)-1,2-dihydrophthalazine-2-carboxamide



C19 H22 N4 O S; Mol wt: 354.4758

ACTION – Potent, noncompetitive AMPA receptor antagonist (IC_{50} = 5 μ M) potentially useful as a neuro-protectant and for the treatment of epilepsy. Within this series of dihydrophthalazines, the following are also described:



Compound	R1	R2	Formula
SYM-2257 [292543]	Me	Me	C ₂₀ H ₂₄ N ₄ OS
SYM-2258 [292544]	Me	Et	C ₂₁ H ₂₆ N ₄ OS
SYM-2260 [292545]	H	Me	C ₁₉ H ₂₂ N ₄ OS
SYM-2261 [292546]	H	Et	C ₂₀ H ₂₄ N ₄ OS
SYM-2262 [292547]	H	H	C ₁₈ H ₂₀ N ₄ OS

SOURCE – Annovis.

REFERENCES

1. Li, B. et al. *Novel sulfur containing dihydrophthalazine antagonists of AMPA receptors.* 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 212.

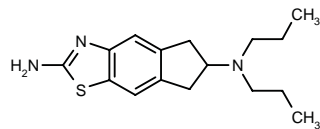
TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

GMC-1111

292658

*N*⁶,*N*⁶-Dipropyl-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]thiazole-2,6-diamine

N-(2-Amino-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]thiazol-6-yl)-*N,N*-dipropylamine



C16 H23 N3 S; Mol wt: 289.4447

ACTION – High-affinity dopamine D3 ligand (K_i = 1.4 nM) with high selectivity over D4 receptors (K_i = 272 nM) and additional lipid peroxidation-inhibitory activity (IC_{50} = 60 μ M in Fe²⁺/ascorbate-treated rat liver microsomes). In an *in vitro* functional assay, compound showed D2L partial agonist activity (EC_{50} = 5.7 nM for stimulating mitogenesis in CHO-L6 cells transfected with D2L receptors) and antagonist activity at D3 receptors (measured as inhibition of quinpirole-induced mitogenesis in CHO-L6 cells). *In vivo*, compound produced a strong and long-lasting activation of rotational behavior in rats with unilateral 6-OHDA lesions following both s.c. and p.o. administration, indicating an agonist effect at postsynaptic dopamine receptors. In addition, compound produced a dose-dependent increase in dopamine turnover in microdialysis experiments in rat striatum. Candidate for further examination as a potential atypical antipsychotic and treatment for Parkinson's disease.

SOURCES – University of Groningen, Groningen (NL); Pfizer; Pharmacia.

REFERENCES

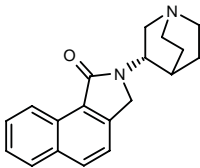
1. Wikström, H.V. et al. *New 2-aminothiazol-fused-2-aminoidans and 2-aminotetralins and their use.* WO 0001680.

2. van Vliet, L.A. et al. *Thiazoloidans and thiazolobenzopyrans: A novel class of orally active central dopamine (partial) agonists.* J Med Chem 2000, 43(19): 3549.

TREATMENT OF NAUSEA AND VOMITING

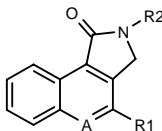
291969

2-[Quinuclidin-3(S)-yl]-2,3-dihydro-1*H*-benzo[*e*]isoindol-1-one



C19 H20 N2 O; Mol wt: 292.3800

ACTION – Potent and selective 5-HT₃ receptor antagonist with subnanomolar affinity for the 5-HT₃ receptor and proven active *in vivo* in the Bezold-Jarisch test in rats at 0.1 mg/kg i.v. This compound is potentially useful as an antiemetic in the treatment of spontaneous, postoperative or chemotherapy-induced nausea and vomiting, and also for the treatment of CNS disorders such as anxiety, panic attacks and depression, and as an antitussive. A representative compound from a series of basic derivatives of benz[*e*]isoindol-1-ones and pyrrolo[3,4-*c*]-quinolin-1-ones, wherein the following are also included:



Compound	R1	R2	A	Formula
291970	H	endo-8-Me-8-azabicyclo[3.2.1]oct-3-yl	CH	C ₂₀ H ₂₂ N ₂ O
291971	H	endo-8-Me-8-azabicyclo[3.2.1]oct-3-yl	N	C ₁₉ H ₂₁ N ₃ O
291972	Cl	endo-8-Me-8-azabicyclo[3.2.1]oct-3-yl	N	C ₁₉ H ₂₀ ClN ₃ O
291973	OPr	endo-8-Me-8-azabicyclo[3.2.1]oct-3-yl	N	C ₂₂ H ₂₇ N ₃ O ₂
291974	OH	endo-8-Me-8-azabicyclo[3.2.1]oct-3-yl	N	C ₁₉ H ₂₁ N ₃ O ₂
291975	H	3-quinuclidinyl	CH	C ₁₉ H ₂₀ N ₂ O
291976	H	3(R)-quinuclidinyl	CH	C ₁₉ H ₂₀ N ₂ O
291977	H	3-quinuclidinyl	N	C ₁₈ H ₁₉ N ₃ O

SOURCE – Rotta.

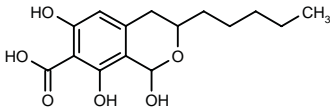
REFERENCES

1. Macovec, F. et al. (Rotta Research Laboratorium SpA) *Novel basic derivs. of benz(e)isoindol-1-ones and pyrrolo(3,4-c)quinolin-1-ones with 5-HT₃-antagonistic activity, their preparation and their therapeutic use.* EP 1018512.

COGNITION-ENHANCING DRUGS

291953

1,6,8-Trihydroxy-3-pentyl-3,4-dihydro-1*H*-2-benzopyran-7-carboxylic acid



C15 H20 O6; Mol wt: 296.3170

ACTION – Isochroman compound produced by fermentation of the fungus *Penicillium simplicissimum* FERM BP-6357 and found to inhibit β-amyloid protein aggregation. Based on this effect, the compound is expected to be of use for the treatment of Alzheimer's disease.

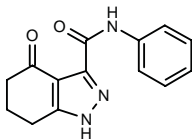
SOURCE – Pfizer.

REFERENCES

1. Hirai, H. et al. (Pfizer Inc.) *Isochroman cpds. and their production process.* EP 1018511, JP 2000198781.

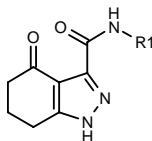
292393

4-Oxo-*N*-phenyl-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxamide



C14 H13 N3 O2; Mol wt: 255.2757

ACTION – Agent for the treatment of cognition disorders that binds selectively to GABA_A α5 receptors, as demonstrated by inhibition of [³H]-flumazenil binding to the benzodiazepine binding site of human GABA_A receptors containing the α5 subunit expressed in Ltk- cells. Other specifically claimed tetrahydroindazole derivatives are:



Compound	R1	Formula
292394	2,5-(F)2-Ph	C ₁₄ H ₁₁ F ₂ N ₃ O ₂
292395	2-Pyr	C ₁₃ H ₁₂ N ₄ O ₂
292396	4-MeO-Ph	C ₁₅ H ₁₈ N ₃ O ₃
292397	4-(NH2CH2CH2)-Ph	C ₁₆ H ₁₈ N ₄ O ₂
292398	4-(MeNHCH2CH2)-Ph	C ₁₇ H ₂₀ N ₄ O ₂
292399	4-(t-BuOCONHCH2)-Ph	C ₂₀ H ₂₄ N ₄ O ₄
292400	4-(NH2CH2)-Ph	C ₁₅ H ₁₆ N ₄ O ₂
292401	4-[N(Me)2CH2CH2]-Ph	C ₁₈ H ₂₂ N ₄ O ₂

Preferably the compounds of the invention are inverse agonists at the GABA_A α 5 subtype and antagonists at the α 1, α 2 and α 3 subtypes.

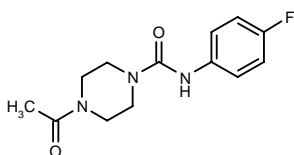
SOURCE – Merck Sharp & Dohme.

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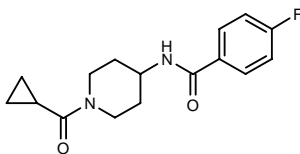
292510

4-Acetyl-N-(4-fluorophenyl)piperazine-1-carboxamide



C13 H16 F N3 O2; Mol wt: 265.2864

ACTION – Cholinergic activity potentiator shown to induce penile erections in rats at 1 mg/kg i.p. Potentially useful for the treatment of amnesia and dementia. Another exemplified amide compound is:



292511: C16 H19 F N2 O2

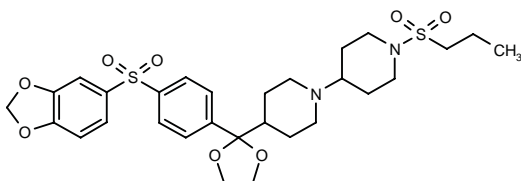
SOURCE – Fujisawa.

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1. Yamada, A. and Aoki, S. (Fujisawa Pharmaceutical Co., Ltd.) *Amide cpds*. WO 0042011.

292664

4-[4-[1-[4-(1,3-Benzodioxol-5-ylsulfonyl)phenyl]-1-(1,3-dioxolan-2-yl)methyl]piperidin-1-yl]-1-(propylsulfonyl)-piperidine



C29 H38 N2 O8 S2; Mol wt: 606.7572

ACTION – Muscarinic M₂ receptor antagonist with high affinity for the M₂ receptor (K_i = 0.010 nM) and high selectivity over M₁ and M₃ receptors (M_1/M_2 = 101.5; M_3/M_2 = 93). Compound induced prolonged release of acetylcholine in rat brain, as demonstrated in microdialysis experiments in rats administered a dose of 10 mg/kg p.o., and it significantly enhanced cognitive performance in rats at doses of 0.1-1 mg/kg p.o., as demonstrated in passive avoidance studies. Potentially useful for improving cognitive deficits in patients with Alzheimer's disease.

SOURCE – Schering-Plough.

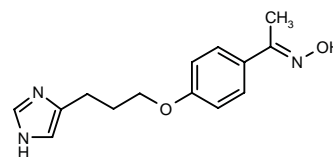
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1. Boyle, C.D. et al. *Benzylidene ketal derivatives as M2 muscarinic receptor antagonists*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 114.

IMOPROXIFAN

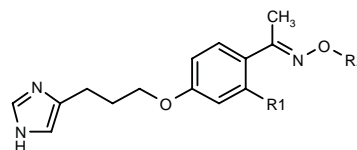
293239

1-[4-[3-(1*H*-Imidazol-4-yl)propoxy]phenyl]ethan-1-one oxime



C14 H17 N3 O2; Mol wt: 259.3073

ACTION – Potent histamine H₃ receptor antagonist (K_i = 0.26 nM in rat cerebral cortex synaptosomes; pA_2 = 8.6 in rat cerebral cortex) with high functional selectivity over H₁ and H₂ receptors (pA_2 = 4.6 and < 4.5, respectively, in guinea pig ileum and atrium) and other neurotransmitter receptors. *In vivo*, compound increased *tele-N*-methyl-histamine levels in mouse brain after p.o. administration (ED₅₀ = 0.034 mg/kg). Potentially useful for the treatment of Alzheimer's disease and attention deficit hyperactivity disorder. Within the imoproxifan series, the following are also described:



Compound	R1	R2	Formula
294026	H	Me	C ₁₅ H ₁₉ N ₃ O ₂
294027	F	H	C ₁₄ H ₁₆ FN ₃ O ₂

SOURCES – Bioprojet; INSERM, Paris Cedex (FR).

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1. Schwartz, J.-C. et al. ([INSERM [Institut National de la Sante et de la Recherche Medicale]; Societe Civile Bioprojet) *Imidazole derivs. as histamine receptor H3 (ant)agonists*. EP 0760811, FR 2732017, JP 1998501001, WO 9629315.

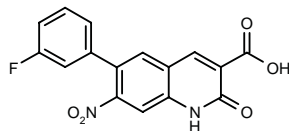
2. Sasse, A. et al. *New histamine H3-receptor ligands of the proxifan series: Imoproxifan and other selective antagonist with high oral in vivo potency*. J Med Chem 2000, 43(17): 3343.

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TREATMENT OF
CEREBROVASCULAR DISEASES

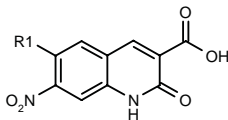
292055

6-(3-Fluorophenyl)-7-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylic acid



C16 H9 F N2 O5; Mol wt: 328.2541

ACTION – Excitatory amino acid receptor antagonist, in particular AMPA antagonist ($K_i = 1.23 \mu\text{M}$), potentially useful in the treatment of cerebrovascular diseases. Other 6-arylquinoline-carboxylate derivatives are:



Compound	R1	Formula
292056	Ph	C ₁₆ H ₁₀ N ₂ O ₅
292057	4-Br-Ph	C ₁₆ H ₉ BrN ₂ O ₅
292058	2-Naph	C ₂₀ H ₁₂ N ₂ O ₅
292059	4-MeO-Ph	C ₁₇ H ₁₂ N ₂ O ₆

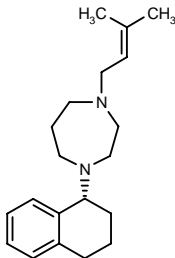
SOURCE – Kyorin.

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1. Takano, Y. et al. (Kyorin Pharmaceutical Co., Ltd.) *6-Arylquinoline carboxylate derivs. and their addition salts, and their preparation method.* JP 2000169450.

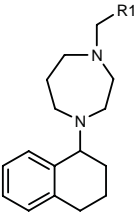
292101

1-(3-Methyl-2-butenyl)-4-[1,2,3,4-tetrahydronaphthalen-1(R)-yl]perhydro-1,4-diazepine



C20 H30 N2; Mol wt: 298.4710

ACTION – Inhibitor of the [³H]-emopamil binding site with potential use in the treatment of neurological disorders such as stroke, head trauma, transient cerebral ischemic attack, Alzheimer’s disease, Parkinson’s disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis and AIDS-related dementia. Other specifically claimed 1,4-diazacycloheptane derivatives are:



Compound	R1	Isomer	Formula
292102	CH=C(Me)2	S	C ₂₀ H ₃₀ N ₂
292103	(S)-CH(OH)Me	R	C ₁₈ H ₂₈ N ₂ O
292104	(R)-CH(OH)Me	R	C ₁₈ H ₂₈ N ₂ O
292105	(S)-CH(OH)Me	S	C ₁₈ H ₂₈ N ₂ O
292106	(R)-CH(OH)Me	S	C ₁₈ H ₂₈ N ₂ O
292107	CH2CH2OH	S	C ₁₈ H ₂₈ N ₂ O
292108	CH2CH2OH	R	C ₁₈ H ₂₈ N ₂ O
292109	(S)-CH(OH)CH2OCH2Ph	R	C ₂₅ H ₃₄ N ₂ O ₂
292110	(R)-CH(OH)CH2OCH2Ph	R	C ₂₅ H ₃₄ N ₂ O ₂
292111	(S)-CH(OH)CH2OCH2Ph	S	C ₂₅ H ₃₄ N ₂ O ₂
292112	(R)-CH(OH)CH2OCH2Ph	S	C ₂₅ H ₃₄ N ₂ O ₂

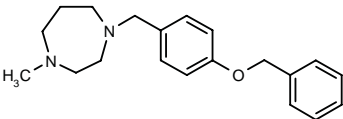
SOURCE – AstraZeneca.

REFERENCES

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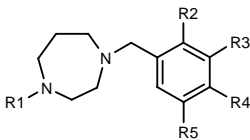
292113

1-[4-(Benzyloxy)benzyl]-4-methylperhydro-1,4-diazepine



C20 H26 N2 O; Mol wt: 310.4384

ACTION – Selective inhibitor of [³H]-emopamil binding, potentially useful for the treatment of neurological disorders such as stroke, head trauma, transient cerebral ischemic attack, Alzheimer’s disease, Parkinson’s disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis and AIDS-related dementia. Other specifically claimed homopiperazine derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
292114	Me	CF3	H	CF3	H	C ₁₅ H ₁₈ F ₆ N ₂
292115	Pr	H	H	OCH2Ph	H	C ₂₂ H ₃₀ N ₂ O
292116	CH2Ph	H	H	OCH2Ph	H	C ₂₆ H ₃₀ N ₂ O
292117	C5H11	H	H	OCH2Ph	H	C ₂₄ H ₃₄ N ₂ O
292118	Me	H	CF3	H	CF3	C ₁₅ H ₁₈ F ₆ N ₂
292119	CH2CH2Ph	H	H	OCH2Ph	H	C ₂₇ H ₃₂ N ₂ O
292120	4-(PhCH2O)-PhCH2	H	F	H	F	C ₂₈ H ₂₈ F ₂ N ₂ O
292121	CH2CH2CF=CF2	H	H	OCH2Ph	H	C ₂₃ H ₂₇ F ₃ N ₂ O
292122	Bu	H	H	OCH2Ph	H	C ₂₃ H ₃₂ N ₂ O
292123	i-Pr	H	H	OCH2Ph	H	C ₂₂ H ₃₀ N ₂ O
292124	i-Bu	H	H	OCH2Ph	H	C ₂₃ H ₃₂ N ₂ O
292125	Et	H	H	OCH2Ph	H	C ₂₁ H ₂₈ N ₂ O
292126	Me	H	H	t-Bu	H	C ₁₇ H ₂₆ N ₂
292127	CH2CH(OH)Me	H	H	OCH2Ph	H	C ₂₂ H ₃₀ N ₂ O ₂

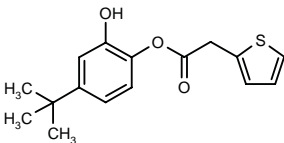
SOURCE – AstraZeneca.

REFERENCES

1. Simpson, T.R. et al. (AstraZeneca UK, Ltd.) *Homopiperazine derivs. as selective emopamil inhibitors*. WO 0039110.

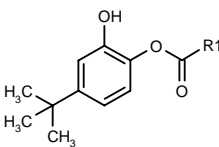
292130

2-(2-Thienyl)acetic acid 4-*tert*-butyl-2-hydroxyphenyl ester



C16 H18 O3 S; Mol wt: 290.3812

ACTION – Poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase) inhibitor, potentially useful in the treatment of diseases involving tissue injury due to necrosis- or apoptosis-induced cell damage or death, ischemia- and/or reperfusion-induced neuronal injury, neurological disorders, neurodegenerative diseases, vascular stroke, cardiovascular disorders, age-related macular degeneration, AIDS and other immune diseases, arthritis, atherosclerosis, cachexia, cancer, neuropathic pain and other diseases induced or exacerbated by cellular senescence. Other specifically claimed *ortho*-diphenol compounds are:



Compound	R1	Formula
292131	2-Cl-Ph	C ₁₇ H ₁₇ ClO ₃
292132	4-Cl-Ph	C ₁₇ H ₁₇ ClO ₃
292133	3,4,5-(MeO)3-Ph	C ₂₀ H ₂₄ O ₆
292134	2-(PhS)-3-Pyr	C ₂₂ H ₂₁ NO ₃ S

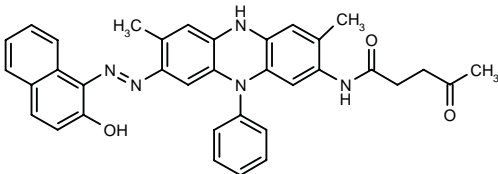
SOURCE – Guilford.

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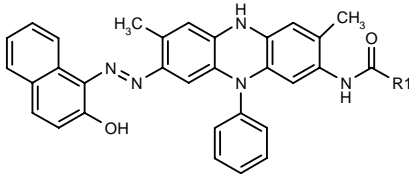
292137

N-[8-[(*E*)-2-(2-Hydroxynaphthalen-1-yl)diazenyl]-3,7-dimethyl-10-phenyl-5,10-dihydrophenazin-2-yl]-4-oxopentanamide



C35 H31 N5 O3; Mol wt: 569.6619

ACTION – Poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase) inhibitor, potentially useful in the treatment of diseases involving tissue injury due to necrosis- or apoptosis-induced cell damage or death, ischemia- and/or reperfusion-induced neuronal injury, neurological disorders, neurodegenerative diseases, vascular stroke, cardiovascular disorders, age-related macular degeneration, AIDS and other immune diseases, arthritis, atherosclerosis, cachexia, cancer, neuropathic pain and other diseases induced or exacerbated by cellular senescence. Other specifically claimed phenazine compounds are:



Compound	R1	Formula
292138	CH(NHCONH2)CH(Me)Et	C ₃₇ H ₃₇ N ₇ O ₃
292139	2-benzofuryl	C ₃₉ H ₂₉ N ₅ O ₃
292140	4,5-(MeO)2-2-NO2-Ph	C ₃₉ H ₃₂ N ₆ O ₆
292141	2-(ClCH2CONH)-4-thiazolyl-C(=NOMe)	C ₃₈ H ₃₁ ClN ₆ O ₄ S
292142	2-NO2-PhCH2	C ₃₈ H ₃₀ N ₆ O ₄

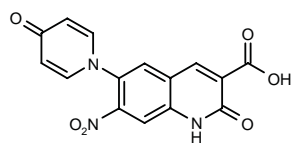
SOURCE – Guilford.

REFERENCES

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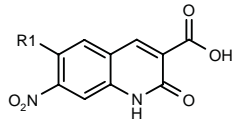
292163

6-(1,4-Dihydro-4-oxopyridin-1-yl)-7-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylic acid



C15 H9 N3 O6; Mol wt: 327.2511

ACTION – Excitatory amino acid receptor antagonist, in particular AMPA receptor antagonist, potentially useful in the treatment of excitatory amino acid-mediated neuronal disorders. Other exemplified compounds from this series of 6,7-disubstituted quinoline carboxylate derivatives are:



Compound	R1	Formula
292164	Cl	C ₁₀ H ₅ ClN ₂ O ₅
292165	Br	C ₁₀ H ₅ BrN ₂ O ₅
292166	Me	C ₁₁ H ₈ N ₂ O ₅
292167	1-imidazolyl	C ₁₃ H ₈ N ₄ O ₅
292168	1-imidazolyl-CH2	C ₁₄ H ₁₀ N ₄ O ₅
292169	N(Me)2	C ₁₂ H ₁₁ N ₃ O ₅

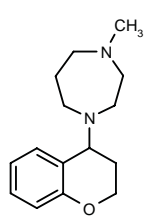
SOURCE – Kyorin.

REFERENCES

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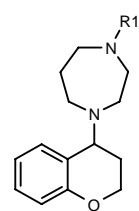
292403

1-(3,4-Dihydro-2*H*-1-benzopyran-4-yl)-4-methylperhydro-1,4-diazepine



C15 H22 N2 O; Mol wt: 246.3518

ACTION – Agent for the treatment or prevention of neurological disorders that selectively binds to the [³H]-emopamil binding site, specifically claimed for the therapy of stroke, head trauma, transient cerebral ischemic attack, Alzheimer’s disease, Parkinson’s disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis and AIDS-related dementia. Other exemplified 1,4-diazacycloheptane compounds are:



Compound	R1	Isomer	Formula
292404	H		C ₁₄ H ₂₀ N ₂ O
292405	H	(+)-(S)	C ₁₄ H ₂₀ N ₂ O
292406	Me	(+)-(S)	C ₁₅ H ₂₂ N ₂ O
292407	H	R	C ₁₄ H ₂₀ N ₂ O
292408	Me	R	C ₁₅ H ₂₂ N ₂ O
292409	i-Pr	S	C ₁₇ H ₂₆ N ₂ O
292410	i-Pr	R	C ₁₇ H ₂₆ N ₂ O
292411	i-BuCH2		C ₁₉ H ₃₀ N ₂ O
292412	Pr		C ₁₇ H ₂₆ N ₂ O
292413	CH2CH=C(Me)2		C ₁₉ H ₂₈ N ₂ O
292414	CH2Ph		C ₂₁ H ₂₆ N ₂ O

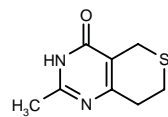
SOURCE – AstraZeneca.

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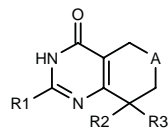
292627

2-Methyl-4,5,7,8-tetrahydro-3*H*-thiopyrano[4,3-*d*]pyrimidin-4-one



C8 H10 N2 O S; Mol wt: 182.2460

ACTION – Poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase) inhibitor (IC₅₀ = 0.21 μM against enzyme from rat brain) with low toxicity, potentially useful in the treatment of stroke, myocardial infarction, diabetes, septic shock, Alzheimer’s disease, Huntington’s chorea, Parkinson’s disease, and as an antiinflammatory agent. Other compounds from this series of pyrimidine derivatives include the following:



Compound	R1	R2	R3	A	Formula
292628	H	H	H	S	C ₇ H ₈ N ₂ OS
292629	Ph	H	H	S	C ₁₃ H ₁₂ N ₂ OS
292630	Me	-CH2-		S	C ₉ H ₁₀ N ₂ OS
292631	Me	-CH2-		CH2	C ₁₀ H ₁₂ N ₂ O
292632	Me	-CH(CH2OMe)-		S	C ₁₁ H ₁₄ N ₂ O ₂ S

SOURCE – Meiji Seika.

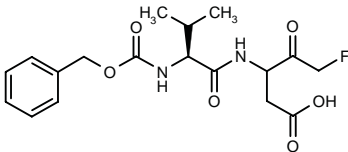
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CV-1013

290832

N-Benzyloxycarbonyl-L-valyl-DL-aspartyl-fluoromethane



C18 H23 F N2 O6; Mol wt: 382.3857

ACTION – Broad-spectrum caspase inhibitor (IC₅₀ = 40 and 60 nM against caspase 3 and 6, respectively) with high selectivity over other cysteine, serine or aspartate proteases. Compound was found to be very active in several whole-cell models of apoptosis, with IC₅₀ values of 100 nM or less. When given i.v. to spontaneous hypertensive rats with transient cerebral ischemia, compound at doses of 20 mg/kg as bolus followed by continuous infusion of 5 mg/kg/h for 6 h induced a statistically significant reduction in cortical infarct volume compared with control animals (13 and 24% of total hemispheric volume, respectively). Potentially useful for the treatment of stroke.

SOURCE – Cytovia (Maxim).

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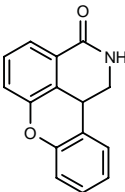
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GPI-6150

270851

1,11b-Dihydro-1-benzopyrano[4,3,2-*de*]isoquinolin-3(2*H*)-one



C15 H11 N O2; Mol wt: 237.2569

ACTION – Potent and competitive inhibitor of poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase; K_i = 60 nM; IC₅₀ = 100 nM) proven to reduce cerebral infarct volume to approximately the same level as in mice whose PARP genes were disrupted, in both transient and permanent focal cerebral ischemia models in rats (75 and 32% reduction, respectively, at 40 mg/kg i.p.). Moreover, in a rat model of regional myocardial ischemia, compound at 4 mg/kg i.p. decreased infarct volume by 40%. Potentially useful for the treatment of ischemia/reperfusion injuries such as cerebrovascular stroke and myocardial infarction.

SOURCE – Guilford.

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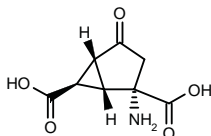
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LY-418426***270548**

(1*S**,2*S**,5*R**,6*R**)-2-Amino-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid



C₈ H₉ N O₅; Mol wt: 199.1611

ACTION – Potent and selective group II metabotropic glutamate receptor agonist ($K_i = 3.74$ and 0.36 nM for binding to $mglu_2$ and $mglu_3$ receptors, respectively), potentially useful for the treatment of a variety of CNS disorders including schizophrenia, anxiety, depression, bipolar disorder, drug addiction, cognitive disorders, Alzheimer's disease, Huntington's disease, Parkinson's disease, movement disorders associated with muscle rigidity, brain ischemia, and spinal cord and head trauma.

SOURCE – Lilly.

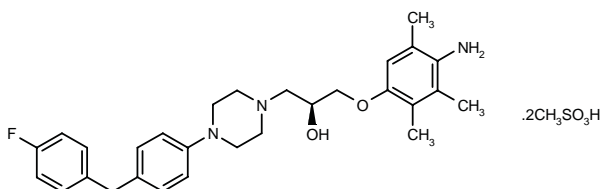
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- Valli, M.J. et al. *Design and synthesis of a novel series of C4-substituted 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylates as potent and selective group II metabotropic glutamate receptor agonists*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 106.

*Identified compound **270548** Drug Data Rep 1999, 021(02): 0122.

SUN-N8075***276717**

1-(4-Amino-2,3,5-trimethylphenoxy)-3-[4-[4-(4-fluorobenzyl)phenyl]piperazin-1-yl]propan-2(*S*)-ol dimethanesulfonate



C₂₉ H₃₆ F N₃ O₂ . 2 C H₄ O₃ S; Mol wt: 669.8316

ACTION – Antiischemic agent, a dual neuronal Na⁺ and T-type Ca²⁺ blocker proven to inhibit veratridine-induced depolarization in rat cerebrocortical synaptosomes ($IC_{50} = 0.42$ μ M) and to block the low-threshold T-type Ca²⁺ currents in primary cultured rat cerebrocortical neurons ($IC_{50} = 2.0$ μ M). Compound was shown to displace [³H]-batrachotoxin binding from neurotoxin binding site 2 of Na⁺ channels, but had no effect on the binding of the site 1 ligand [³H]-saxitoxin. Moreover, compound displays antioxidant activity, measured as suppression of lipid peroxidation in rat cerebrocortical membranes ($IC_{50} = 0.31$ μ M). Unlike other Na⁺ channel blockers, it had no binding affinity for dopamine D2 receptors. *In vivo*, compound

showed anticonvulsant activity against audiogenic seizures in DBA/2 mice ($ED_{50} = 6.5$ mg/kg i.p.) and neuroprotective activity in a transient focal ischemia model of middle cerebral artery occlusion in rats, where it significantly reduced infarct size (67.9% reduction with respect to control group) when given at a dose of 3 mg/kg i.v. immediately after both occlusion and reperfusion; at effective doses it did not produce changes in systemic blood pressure or heart rate.

SOURCE – Suntory.

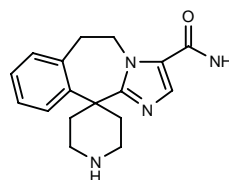
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- Annoura, H. et al. (Suntory Ltd.) *Arylpiperidinopropanol and arylpiperazinopropanol derivs. and pharmaceuticals containing the same*. CA 2276373, EP 0958280, WO 9923072.
- Annoura, H. et al. *Discovery of (2*S*)-1-(4-amino-2,3,5-trimethylphenoxy)-3-(4-[4-(4-fluorobenzyl)phenyl]-1-piperazinyl)-2-propanol dimethanesulfonate (SUN N8075): A dual Na⁺ and Ca²⁺ channel blocker with antioxidant activity*. J Med Chem 2000, 43(18): 3372.
- Annoura, H. et al. *Discovery of novel neuroprotectants Na⁺ and Ca²⁺ channel dual blockers with antioxidant activity*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-103.

*Identified compound **276717** Drug Data Rep 1999, 021(07): 0588.

RESPIRATORY DRUGS**TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS****291896**

5,6-Dihydrospiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4'-piperidine]-3-carboxamide

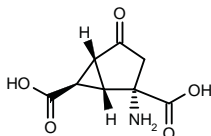


C₁₇ H₂₀ N₄ O; Mol wt: 296.3720

ACTION – Antihistaminic agent with selective binding affinity for histamine H₁ receptors and very low affinity for 5-HT_{2A} and 5-HT_{2C} receptors, proven to protect rats from compound 48/80-induced lethality with an ED_{50} of 0.04 mg/kg p.o. The compound is characterized by the absence of relevant appetite stimulation, weight gain, sedation or cardiohemodynamic and electrophysiological effects. Its pharmacological properties and favorable duration of action make it useful for once-daily administration in the treatment of allergic diseases. Other exemplified spiro compounds include the following:

LY-418426***270548**

(1*S**,2*S**,5*R**,6*R**)-2-Amino-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid



C₈ H₉ N O₅; Mol wt: 199.1611

ACTION – Potent and selective group II metabotropic glutamate receptor agonist ($K_i = 3.74$ and 0.36 nM for binding to $mglu_2$ and $mglu_3$ receptors, respectively), potentially useful for the treatment of a variety of CNS disorders including schizophrenia, anxiety, depression, bipolar disorder, drug addiction, cognitive disorders, Alzheimer's disease, Huntington's disease, Parkinson's disease, movement disorders associated with muscle rigidity, brain ischemia, and spinal cord and head trauma.

SOURCE – Lilly.

REFERENCES

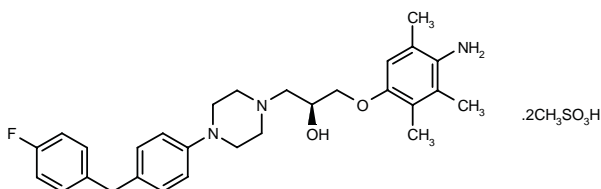
1. Massey, S.M. et al. (Eli Lilly and Company) *Excitatory amino acid receptor modulators*. EP 0878463, US 5958960.

2. Valli, M.J. et al. *Design and synthesis of a novel series of C4-substituted 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylates as potent and selective group II metabotropic glutamate receptor agonists*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 106.

*Identified compound **270548** Drug Data Rep 1999, 021(02): 0122.

SUN-N8075***276717**

1-(4-Amino-2,3,5-trimethylphenoxy)-3-[4-[4-(4-fluorobenzyl)phenyl]piperazin-1-yl]propan-2(*S*)-ol dimethanesulfonate



C₂₉ H₃₆ F N₃ O₂ . 2 C H₄ O₃ S; Mol wt: 669.8316

ACTION – Antiischemic agent, a dual neuronal Na⁺ and T-type Ca²⁺ blocker proven to inhibit veratridine-induced depolarization in rat cerebrocortical synaptosomes ($IC_{50} = 0.42$ μ M) and to block the low-threshold T-type Ca²⁺ currents in primary cultured rat cerebrocortical neurons ($IC_{50} = 2.0$ μ M). Compound was shown to displace [³H]-batrachotoxin binding from neurotoxin binding site 2 of Na⁺ channels, but had no effect on the binding of the site 1 ligand [³H]-saxitoxin. Moreover, compound displays antioxidant activity, measured as suppression of lipid peroxidation in rat cerebrocortical membranes ($IC_{50} = 0.31$ μ M). Unlike other Na⁺ channel blockers, it had no binding affinity for dopamine D₂ receptors. *In vivo*, compound

showed anticonvulsant activity against audiogenic seizures in DBA/2 mice ($ED_{50} = 6.5$ mg/kg i.p.) and neuroprotective activity in a transient focal ischemia model of middle cerebral artery occlusion in rats, where it significantly reduced infarct size (67.9% reduction with respect to control group) when given at a dose of 3 mg/kg i.v. immediately after both occlusion and reperfusion; at effective doses it did not produce changes in systemic blood pressure or heart rate.

SOURCE – Suntory.

REFERENCES

1. Annoura, H. et al. (Suntory Ltd.) *Arylpiperidinopropanol and arylpiperazinopropanol derivs. and pharmaceuticals containing the same*. CA 2276373, EP 0958280, WO 9923072.

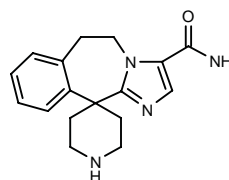
2. Annoura, H. et al. *Discovery of (2*S*)-1-(4-amino-2,3,5-trimethylphenoxy)-3-(4-[4-(4-fluorobenzyl)phenyl]-1-piperazinyl)-2-propanol dimethanesulfonate (SUN N8075): A dual Na⁺ and Ca²⁺ channel blocker with antioxidant activity*. J Med Chem 2000, 43(18): 3372.

3. Annoura, H. et al. *Discovery of novel neuroprotectants Na⁺ and Ca²⁺ channel dual blockers with antioxidant activity*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-103.

*Identified compound **276717** Drug Data Rep 1999, 021(07): 0588.

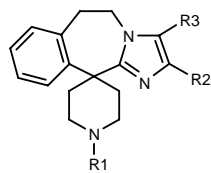
RESPIRATORY DRUGS**TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS****291896**

5,6-Dihydrospiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4'-piperidine]-3-carboxamide

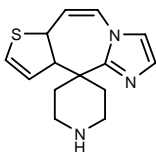


C₁₇ H₂₀ N₄ O; Mol wt: 296.3720

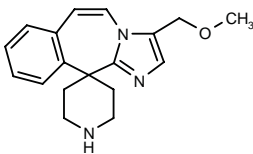
ACTION – Antihistaminic agent with selective binding affinity for histamine H₁ receptors and very low affinity for 5-HT_{2A} and 5-HT_{2C} receptors, proven to protect rats from compound 48/80-induced lethality with an ED_{50} of 0.04 mg/kg p.o. The compound is characterized by the absence of relevant appetite stimulation, weight gain, sedation or cardiohemodynamic and electrophysiological effects. Its pharmacological properties and favorable duration of action make it useful for once-daily administration in the treatment of allergic diseases. Other exemplified spiro compounds include the following:



Compound	R1	R2	R3	Formula
291897	Me	H	H	C ₁₇ H ₂₁ N ₃
291898	Bu	H	H	C ₂₀ H ₂₇ N ₃
291899	H	H	CH2OH	C ₁₇ H ₂₁ N ₃ O
291900	H	H	Cl	C ₁₆ H ₁₈ ClN ₃
291901	H	CONH2	CONH2	C ₁₈ H ₂₁ N ₅ O ₂
291904	CH2CH2OH	H	CONH2	C ₁₉ H ₂₄ N ₄ O ₂
291905	CH2CH(Ph)CO2Et	H	CONH2	C ₂₈ H ₃₂ N ₄ O ₃
291906	CO2Me	H	CONH2	C ₁₉ H ₂₂ N ₄ O ₃
291907	Me	H	CONH2	C ₁₈ H ₂₂ N ₄ O



291902: C14 H17 N3 S



291903: C18 H21 N3 O

SOURCE – Janssen.

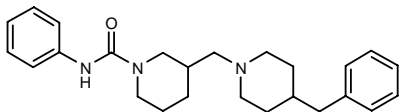
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ASTHMA THERAPY

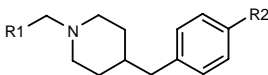
291687

(±)-3-(4-Benzylpiperidin-1-ylmethyl)-N-phenylpiperidine-1-carboxamide

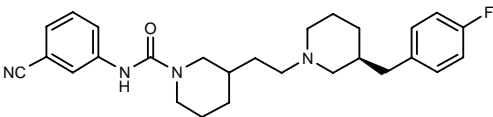


C25 H33 N3 O; Mol wt: 391.5557

ACTION – Chemokine receptor modulator, particularly active at the CCR3 receptor, potentially useful for the treatment of inflammatory disorders, preferably asthma, allergic rhinitis, atopic dermatitis and inflammatory bowel disease. Other specifically claimed nitrogen-containing heterocyclic compounds include the following:



Compound	R1	R2	Formula
291688	1-(3-CO2Et-PhNHCO)-3-Pip	F	C ₂₈ H ₃₆ FN ₃ O ₃
291689	1-(3-CO2Et-PhNHCO)-2-Pip-CH2	F	C ₂₉ H ₃₈ FN ₃ O ₃
291690	1-(PhNHCO)-3-(PhCH2)-3-Pip	F	C ₃₂ H ₃₈ FN ₃ O
291691	2-(PhCH2SO2)-1,2,3,4-tetrahydro-3-isoquinolinyl	F	C ₂₉ H ₃₃ FN ₂ O ₂ S
291692	2-(PhNHCO)-1,2,3,4-tetrahydro-4-isoquinolinyl-CH2	H	C ₃₀ H ₃₅ N ₃ O



291693: C27 H33 F N4 O

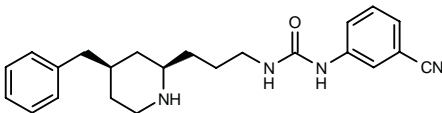
SOURCE – DuPont Pharmaceuticals.

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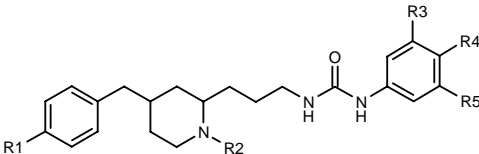
291694

(±)-cis-N-[3-(4-Benzylpiperidin-2-yl)propyl]-N'-(3-cyanophenyl)urea



C23 H28 N4 O; Mol wt: 376.5012

ACTION – Chemokine receptor modulator, particularly active at the CCR3 receptor, potentially useful for the treatment of inflammatory disorders, preferably asthma, allergic rhinitis, atopic dermatitis and inflammatory bowel disease. Other specifically claimed nitrogen-containing heterocyclic compounds include the following:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
291695	F	Pr	H	H	Ac	(±)-trans	C ₂₇ H ₃₆ FN ₃ O ₂
291696	H	Me	H	H	Ac	(±)-trans	C ₂₆ H ₃₃ N ₃ O ₂
291697	H	H	H		-CH=NNH-	(±)-trans	C ₂₃ H ₂₉ N ₅ O
291698	F	Pr	Ac	H	Ac	2S	C ₂₉ H ₃₈ FN ₃ O ₃
291699	F	Pr	1-Me-5-tetrazolyl	H	1-Me-5-tetrazolyl	2S,4R	C ₂₉ H ₃₈ FN ₁₁ O
291700	F	(CH2)3OH	Ac	H	Ac	2S,4R	C ₂₉ H ₃₈ FN ₃ O ₄

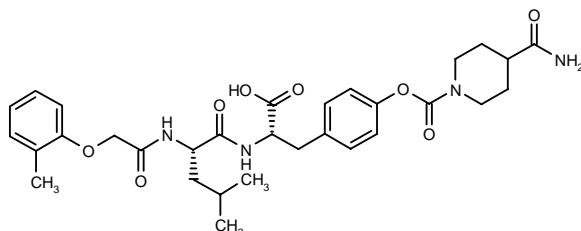
SOURCE – DuPont Pharmaceuticals.

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1. Watson, P.S. et al. (DuPont Pharmaceuticals Co.) *2-Substd.-4-nitrogen heterocycles as modulators of chemokine receptor activity*. WO 0035876.

291780

3-[4-(4-Carbamoylpiperidin-1-ylcarbonyloxy)phenyl]-2(*S*)-[4-methyl-2(*S*)-[2-(2-methylphenoxy)acetamido]pentan-amido]propionic acid



C31 H40 N4 O8; Mol wt: 596.6770

ACTION – Antiinflammatory agent, an antagonist of both $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins, useful for the treatment of inflammatory disorders and particularly preferred for the therapy of asthma, chronic obstructive pulmonary disease and inflammatory diseases of the upper respiratory tract including seasonal and perennial rhinitis. The compound inhibited the interaction of VCAM-1 with Jurkat cells expressing VLA-4 integrin ($\text{pIC}_{50} = 8.55$) and the adhesion of MAdCAM-1 with integrin $\alpha_4\beta_7$ expressed on human B-lymphoid RPMI 886 cell membranes ($\text{pIC}_{50} = 7.5$). It was also active in a CD3/VCAM-1 costimulation of T-lymphocyte proliferation assay. In ovalbumin-sensitized guinea pigs, intratracheal administration of the compound given 0.5 h before and 6 h after antigen challenge produced inhibition of airways hyperreactivity and lung eosinophil infiltration (88 and 58%, respectively, at 0.2 $\mu\text{g/kg}$; 87 and 90%, respectively, at 2 $\mu\text{g/kg}$).

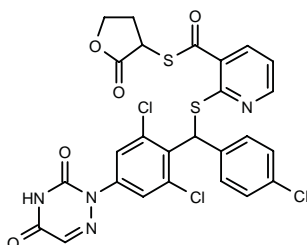
SOURCE – Glaxo Wellcome.

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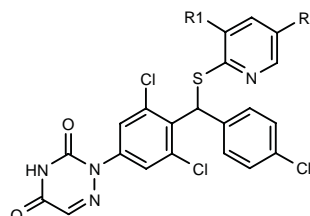
291801

2-[1-(4-Chlorophenyl)-1-[2,6-dichloro-4-(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl)phenyl]methylsulfanyl]-pyridine-3-carbothioic acid *S*-(2-oxotetrahydrofuran-3-yl) ester



C26 H17 Cl3 N4 O5 S2; Mol wt: 635.9343

ACTION – Antiinflammatory agent, an IL-5 inhibitor that also inhibits the production of monocyte chemotactic proteins MCP-1 and MCP-3, while having little or no effect on the production of other chemokines such as IL-1, IL-2, IL-3, IL-4, IL-6, IL-10, interferon gamma and GM-CSF, indicating that it does not act as a broad-spectrum immunosuppressant. The compound is expected to be of use for the treatment of eosinophil-dependent inflammatory diseases, especially bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis. Other exemplified 6-azauracil derivatives are:



Compound	R1	R2	Formula
291802	4-(CO ₂ EtCH ₂)-1-Piz-CH ₂	H	C ₃₀ H ₂₉ Cl ₃ N ₆ O ₄ S
291803	1-(CO ₂ EtCH ₂)-1-Pip-N(Me)CH ₂	H	C ₃₂ H ₃₃ Cl ₃ N ₆ O ₄ S
291804	H	3-CO ₂ H-1-azetidiny-CH ₂	C ₂₆ H ₂₀ Cl ₃ N ₅ O ₄ S
291805	CH ₂ NHCH ₂ CO ₂ Et	H	C ₂₆ H ₂₂ Cl ₃ N ₅ O ₄ S
291806	2-oxo-1,3-dioxol-4-yl-CH ₂ OCO	H	C ₂₆ H ₁₅ Cl ₃ N ₄ O ₇ S

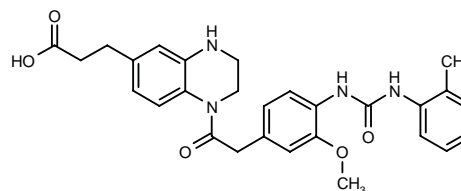
SOURCE – Janssen.

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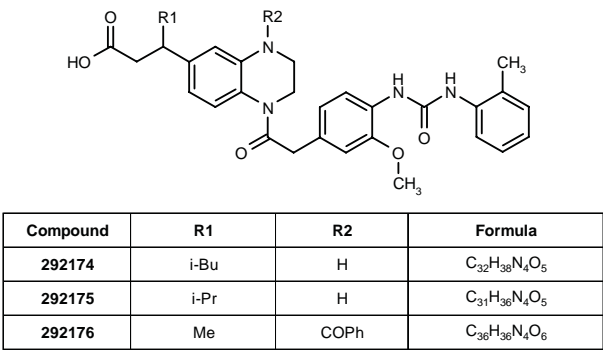
292173

3-[1-[2-[3-Methoxy-4-[3-(2-methylphenyl)ureido]-phenyl]acetyl]-1,2,3,4-tetrahydroquinoxalin-6-yl]propionic acid



C28 H30 N4 O5; Mol wt: 502.5680

ACTION – Inhibitor of VCAM-1 and fibronectin binding to VLA-4 ($\alpha_4\beta_1$) integrin, potentially useful in the treatment of diseases mediated by $\alpha_4\beta_1$ -regulated cell adhesion such as inflammatory diseases, especially asthma. Other exemplified compounds from a series of dihydrobenzo-[1,4]oxazines and tetrahydroquinoxalines are:



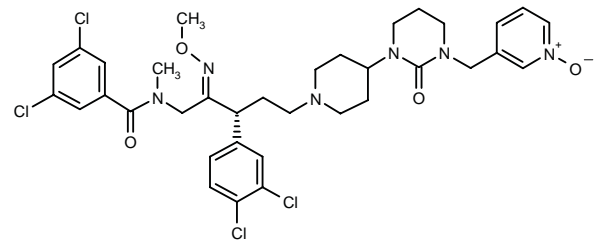
SOURCE – Aventis Pharma.

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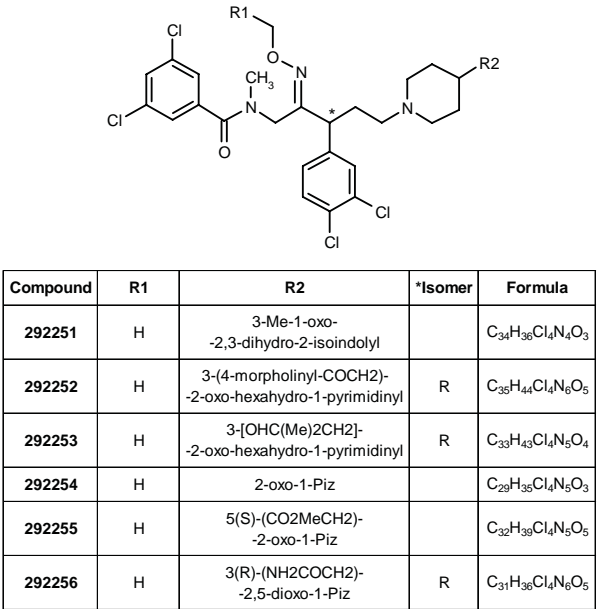
292250

3,5-Dichloro-N-[3(R)-(3,4-dichlorophenyl)-2(Z)-(methoxyimino)-5-[4-[3-(1-oxidopyridin-3-ylmethyl)-2-oxohexahydropyrimidin-1-yl]piperidin-1-yl]pentyl]-N-methylbenzamide

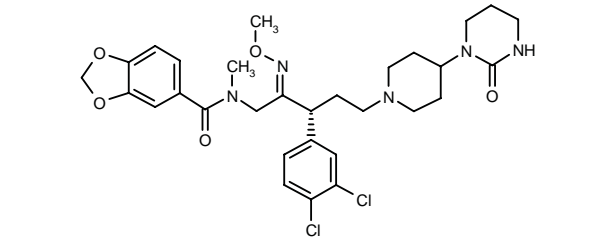


C35 H40 Cl4 N6 O4; Mol wt: 750.5510

ACTION – Neurokinin antagonist with affinity for NK₁, NK₂ and NK₃ receptors (K_i = 0.4 nM), potentially useful in the treatment of respiratory diseases such as asthma, cough and bronchospasm, inflammatory diseases, emesis, depression, gastrointestinal disorders, bladder disorders, atherosclerosis, fibrosing disorders and obesity. Other exemplified compounds are:



Compound	R1	R2	*Isomer	Formula
292258	C(=NOH)-NH2	3-[HON=C(NH2)CH2]-2-oxo-hexahydro-1-pyrimidinyl	R	C ₃₂ H ₄₁ Cl ₄ N ₉ O ₅
292259	H	2-oxo-2,3-dihydro-1-benzimidazolyl	R	C ₃₂ H ₃₃ Cl ₄ N ₅ O ₃
292260	H	3-[CO2HC(Me)2]-2-oxo-hexahydro-1-pyrimidinyl	R	C ₃₃ H ₄₁ Cl ₄ N ₅ O ₅
292261	H	3-(2H-tetrazol-5-yl-CH2)-2-oxo-hexahydro-1-pyrimidinyl	R	C ₃₁ H ₃₇ Cl ₄ N ₉ O ₃



292257: C30 H37 Cl2 N5 O5

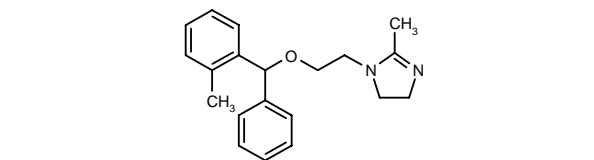
SOURCE – Schering-Plough.

REFERENCES

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292315

2-Methyl-1-[2-[1-(2-methylphenyl)-1-phenylmethoxy]ethyl]-4,5-dihydro-1 H-imidazole



C20 H24 N2 O; Mol wt: 308.4226

ACTION – Potent and selective muscarinic M₃ receptor antagonist with pA₂ values of 9.2, 8.5 and 9.1 against carbachol-induced guinea pig trachea, bladder and ileum contractions, respectively. Potentially useful for the treatment of respiratory disorders such as chronic obstructive pulmonary disease, chronic bronchitis, asthma and rhinitis, gastrointestinal diseases such as irritable bowel syndrome and colitis, renal diseases such as urinary incontinence and pollakiuria, and CNS disorders such as nausea and vomiting.

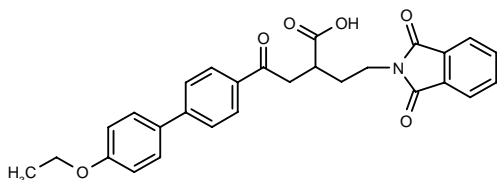
SOURCE – Mitsubishi-Tokyo Pharmaceuticals.

REFERENCES

1. Miura, M. et al. (Mitsubishi-Tokyo Pharmaceuticals, Inc.) 2-Methylimidazoline cpds. WO 0039096.

292355

2-[2-(1,3-Dioxo-2,3-dihydro-1*H*-isoindol-2-yl)ethyl]-4-(4'-ethoxybiphenyl-4-yl)-4-oxobutyric acid



C28 H25 N O6; Mol wt: 471.5065

ACTION – A preferred compound within a series of biarylalkanoic acid derivatives that inhibit matrix metalloproteinases. The compound was selective for MMP-2 (gelatinase A), MMP-3 (stromelysin), MMP-8 (neutrophil collagenase) and MMP-13 (human collagenase 3), giving respective IC_{50} values of 3.2, 60, 21.6 and 70 nM, and for MMP-9 (gelatinase B) and MMP-12 (macrophage elastase), giving K_i values of 1.2 and 0.03 nM, respectively, over MMP-1 (interstitial collagenase; $K_i > 3000$ nM) and MMP-7 (matrilysin; 38% inhibition at 30 nM). Potentially useful for the treatment of respiratory diseases including asthma, chronic obstructive pulmonary disease, chronic bronchitis, emphysema, cystic fibrosis, ARDS, allergic rhinitis, pulmonary fibrotic diseases, pulmonary sarcoidosis and silicosis.

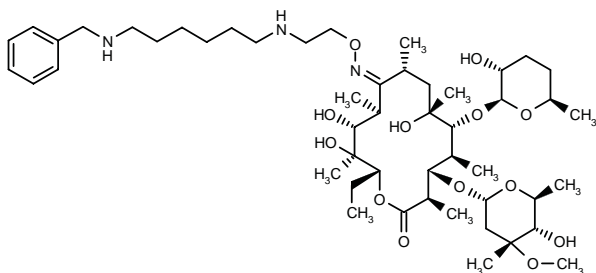
SOURCE – Bayer.

REFERENCES

1. Fitzgerald, M.F. et al. (Bayer AG) *Use of substd. 4-biarylbutyric and 5-biarylpentanoic acid derivs. as matrix metalloprotease inhibitors for the treatment of respiratory diseases.* WO 0040539.

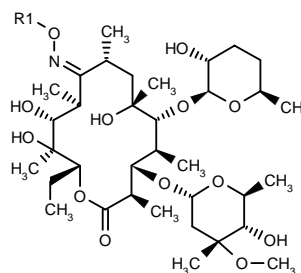
292450

3'-De(dimethylamino)erythromycin A (*E*)-9-[*O*-[2-[6-(benzylamino)hexylamino]ethyl]oxime]



C50 H87 N3 O13; Mol wt: 938.2453

ACTION – Antiinflammatory macrolide that is devoid of antibiotic activity. The antiinflammatory activity was evaluated *in vitro* as inhibition of superoxide anion release ($IC_{50} = 3.5 \pm 0.5$ μ M). The compound also produced 96% inhibition of lipopolysaccharide-induced neutrophilia in bronchoalveolar lavage fluid in rats after repeated i.p. administration. Other exemplified des(dimethylamino) macrolides are:



Compound	R1	Formula
292451	H	C ₃₅ H ₆₃ NO ₁₃
292452	CH ₂ CH ₂ NH(CH ₂) ₆ NH ₂	C ₄₃ H ₈₁ N ₃ O ₁₃

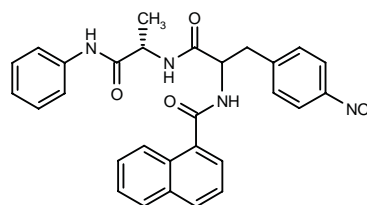
SOURCE – Zambon.

REFERENCES

1. Pellacini, F. et al. (Zambon Group SpA) *Macrolides with anti-inflammatory activity.* WO 0042055.

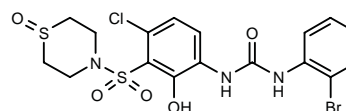
292453

2(*S*)-[2-(1-Naphthylcarboxamido)-3-(4-nitrophenyl)-propionamido]-*N*-phenylpropionamide



C29 H26 N4 O5; Mol wt: 510.5474

ACTION – Chemokine CCR3 receptor antagonist, potentially useful for the treatment of allergic disorders including but not limited to bronchial asthma, eczema, conjunctivitis, allergic rhinitis, nasal polyposis, atopic dermatitis, pruritus and inflammatory bowel disease. Another specifically claimed compound is:



292454: C17 H17 Br Cl N3 O5 S2

SOURCE – SmithKline Beecham.

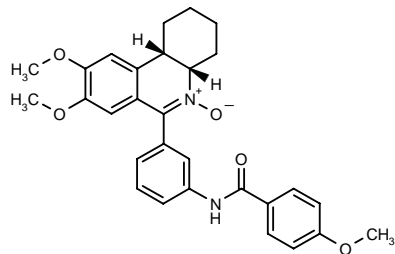
REFERENCES

1. Dhanak, D. (SmithKline Beecham Corp.) *CCR-3 receptor antagonists.* WO 0041685.

292465

(–)-*cis*-8,9-Dimethoxy-6-[3-(4-methoxybenzamido)-phenyl]-1,2,3,4,4a,10b-hexahydrophenanthridine-5-oxide

(–)-*cis*-*N*-[3-(8,9-Dimethoxy-5-oxido-1,2,3,4,4a,10b-hexahydrophenanthridin-6-yl)phenyl]-4-methoxybenzamide



C29 H30 N2 O5; Mol wt: 486.5650

ACTION – A representative compound from a series of phenanthridine *N*-oxides with phosphodiesterase type 4 (PDE4)-inhibitory activity, giving a –log IC₅₀ value of 6.73 in *in vitro* assays. Potentially useful for the treatment of airways disorders such as bronchitis, bronchial asthma, emphysema and chronic obstructive pulmonary disease.

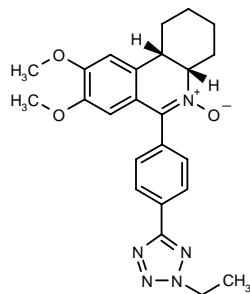
SOURCE – Byk Gulden.

REFERENCES

1. Flockerzi, D. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Phenanthridine-N-oxides with PDE-IV inhibiting activity*. WO 0042017.

292466

(–)-*cis*-6-[4-(2-Ethyl-2*H*-tetrazol-5-yl)phenyl]-8,9-dimethoxy-1,2,3,4,4a,10b-hexahydrophenanthridine-5-oxide



C24 H27 N5 O3; Mol wt: 433.5093

ACTION – A representative compound from a series of phenanthridine *N*-oxides with phosphodiesterase type 4 (PDE4)-inhibitory activity, giving a –log IC₅₀ value of 6.29 in *in vitro* assays. Potentially useful for the treatment of airways disorders such as bronchitis, bronchial asthma, emphysema and chronic obstructive pulmonary disease.

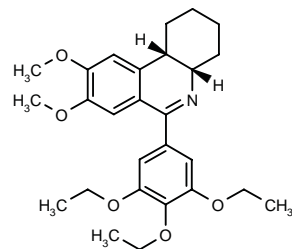
SOURCE – Byk Gulden.

REFERENCES

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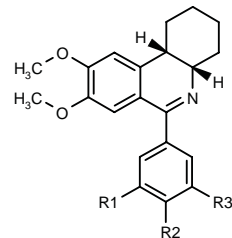
292467

(–)-*cis*-8,9-Dimethoxy-6-(3,4,5-triethoxyphenyl)-1,2,3,4,4a,10b-hexahydrophenanthridine



C27 H35 N O5; Mol wt: 453.5755

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor with a –log IC₅₀ value of 7.81 in *in vitro* assays. Potentially useful for the treatment of airways disorders such as bronchitis, bronchial asthma, emphysema and chronic obstructive pulmonary disease. Other exemplified poly-substituted 6-phenylphenanthridines are:



Compound	R1	R2	R3	Formula
292468	NO2	NO2	H	C ₂₁ H ₂₁ N ₃ O ₆
292469	F	H	F	C ₂₁ H ₂₁ F ₂ NO ₂
292470	NO2	H	NO2	C ₂₁ H ₂₁ N ₃ O ₆
292471	OMe	OMe	OMe	C ₂₄ H ₂₉ NO ₅
292472	SO2Me	OMe	OMe	C ₂₄ H ₂₉ NO ₆ S

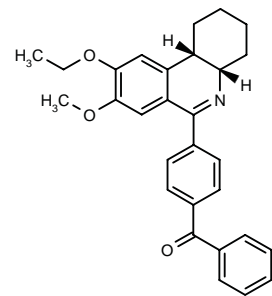
SOURCE – Byk Gulden.

REFERENCES

1. Flockerzi, D. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Polysubstd. 6-phenylphenanthridines with PDE-IV inhibiting activity*. WO 0042018.

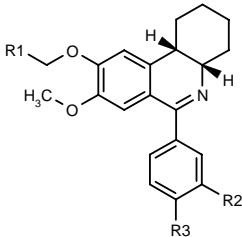
292473

(–)-*cis*-4-(9-Ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydrophenanthridin-6-yl)benzophenone



C29 H29 N O3; Mol wt: 439.5521

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor with a –log IC₅₀ value of 8.87 in *in vitro* assays. Potentially useful for the treatment of airways disorders such as bronchitis, bronchial asthma, emphysema and chronic obstructive pulmonary disease. Other exemplified phenylphenanthridines include the following:



Compound	R1	R2	R3	Formula
292474	H	COPh	H	C ₂₈ H ₂₇ NO ₃
292475	Me	H	CH2Cl	C ₂₃ H ₂₆ ClNO ₂
292476	H	H	4-MeO-PhO	C ₂₈ H ₂₉ NO ₄
292477	Me	cyclopropyl-CH2O	OEt	C ₂₈ H ₃₆ NO ₄
292478	Me	cyclopropyl-CH2O	cyclopropyl-CH2O	C ₃₀ H ₃₇ NO ₄

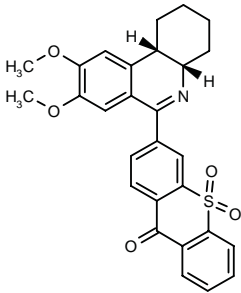
SOURCE – Byk Gulden.

REFERENCES

1. Flockerzi, D. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Phenylphenanthridines with PDE-IV inhibiting activity*. WO 0042020.

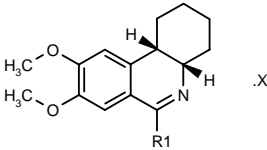
292479

(–)-*cis*-3-(8,9-Dimethoxy-1,2,3,4,4a,10b-hexahydrophenanthridin-6-yl)-9*H*-thioxanthen-9-one *S,S*-dioxide



C28 H25 N O5 S; Mol wt: 487.5735

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor giving a –log IC₅₀ value of 8.39 in *in vitro* assays. Potentially useful for the treatment of airways disorders such as bronchitis, bronchial asthma, emphysema and chronic obstructive pulmonary disease. Other exemplified 6-arylphenanthridines are:



Compound	R1	X	Formula
292480	1,3-benzodioxol-5-yl		C ₂₂ H ₂₃ NO ₄
292481	6-quinolyl		C ₂₄ H ₂₄ N ₂ O ₂
292482	1,4-benzodioxan-6-yl		C ₂₃ H ₂₅ NO ₄
292483	5-benzotriazolyl		C ₂₁ H ₂₂ N ₄ O ₂
292484	2-Naph		C ₂₅ H ₂₅ NO ₂
292487	9-oxo-2-fluorenyl	HCl	C ₂₈ H ₂₅ NO ₃ ·HCl
292488	9,10-anthraquinon-2-yl		C ₂₈ H ₂₅ NO ₄
292489	5-benzimidazolyl		C ₂₂ H ₂₃ N ₃ O ₂
292490	2-Me-6-benzimidazolyl		C ₂₃ H ₂₅ N ₃ O ₂
292491	2- <i>i</i> -Pr-7-(CHF2O)-4-benzofuryl		C ₂₇ H ₂₉ F ₂ NO ₄

SOURCE – Byk Gulden.

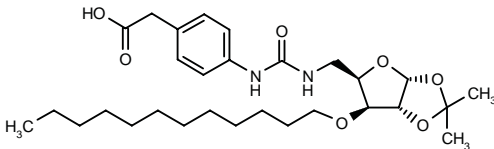
REFERENCES

1. Flockerzi, D. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *6-Arylphenanthridines with PDE-IV inhibiting activity*. WO 0042019.

292529

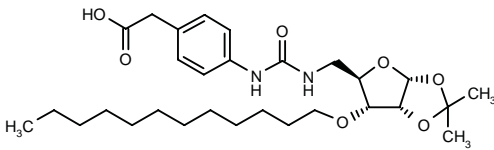
2-[4-[*N*'-(5-Deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)ureido]phenyl]acetic acid

5-[*N*'-[4-(Carboxymethyl)phenyl]ureido]-5-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose

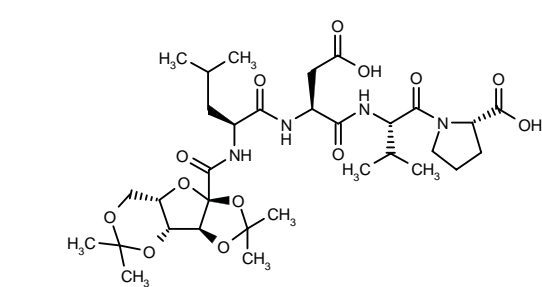


C29 H46 N2 O7; Mol wt: 534.6894

ACTION – VLA-4-mediated cell adhesion inhibitor that is useful for the treatment of autoimmune and inflammatory diseases such as bronchial asthma, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, psoriasis and allograft rejection. The compound demonstrated inhibitory activity in an *in vitro* cell adhesion assay and antiinflammatory activity in the ear swelling test in mice when administered i.v., s.c. and p.o., with respective ED₃₀ values of 10 μg/kg, 500 ng/kg and 1 μg/kg. Other exemplified mono-saccharide derivatives include the following:



292530: C29 H46 N2 O7



292531: C32 H50 N4 O13

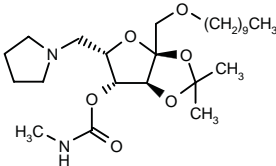
SOURCE – Ranbaxy.

REFERENCES

1. Arora, S.K. et al. (Ranbaxy Laboratories Ltd.) *Derivs. of monosaccharides as cell adhesion inhibitors*. WO 0042053.

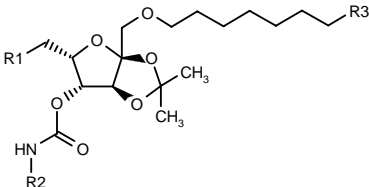
292593

1-*O*-Decyl-6-deoxy-2,3-isopropylidene-4-*O*-(*N*-methyl-carbamoyl)-6-(1-pyrrolidiny)- α -L-xylo-2-hexulofuranose



C25 H46 N2 O6; Mol wt: 470.6464

ACTION – Cell adhesion inhibitor, a VLA-4 antagonist with potential utility in the treatment of autoimmune and inflammatory diseases such as bronchial asthma, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, psoriasis and allograft rejection. Other specifically claimed 2,3-*O*-isopropylidene derivatives of monosaccharides include the following:



Compound	R1	R2	R3	Formula
292594	4-morpholinyl	Ph	Pr	C ₃₀ H ₄₈ N ₂ O ₇
292595	1-Pip	4-NO ₂ -Ph	H	C ₂₈ H ₄₃ N ₃ O ₈
292596	2-Et-1-pyrrolidinyl	4-MeO-Ph	Pr	C ₃₃ H ₅₄ N ₂ O ₇
292597	2-Et-4-morpholinyl	4-Me-Ph	C ₅ H ₁₁	C ₃₅ H ₅₈ N ₂ O ₇
292598	4-morpholinyl	Me	H	C ₂₂ H ₄₀ N ₂ O ₇

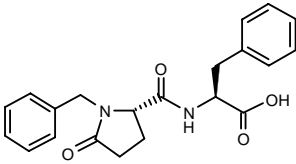
SOURCE – Ranbaxy.

REFERENCES

1. Arora, S.K. et al. (Ranbaxy Laboratories Ltd.) *2,3-O-Isopropylidene derivs. of monosaccharides as cell adhesion inhibitors*. WO 0042054.

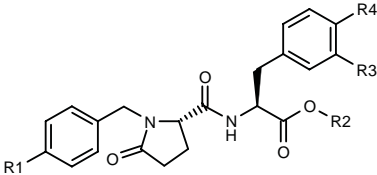
292927

N-Benzyl-L-pyroglutamyl-L-phenylalanine

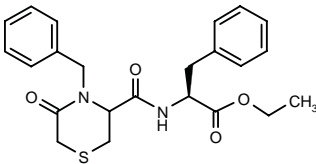


C21 H22 N2 O4; Mol wt: 366.4148

ACTION – Inhibitor of VLA-4-mediated leukocyte adhesion, potentially useful for the treatment of inflammatory diseases such as asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis and myocardial ischemia. Other specifically claimed pyroglutamic acid derivatives include the following:



Compound	R1	R2	R3	R4	Formula
292928	Me	Me	H	NHCOPh	C ₃₀ H ₃₁ N ₃ O ₅
292930	H	H	H	OH	C ₂₁ H ₂₂ N ₂ O ₅
292931	H	t-Bu	H	OCON(Me) ₂	C ₂₈ H ₃₅ N ₃ O ₆
292932	H	Me	Cl	OCON(Me) ₂	C ₂₅ H ₂₈ ClN ₃ O ₆
292933	F	H	H	OCON(Me) ₂	C ₂₄ H ₂₆ FN ₃ O ₆



292929: C23 H26 N2 O4 S

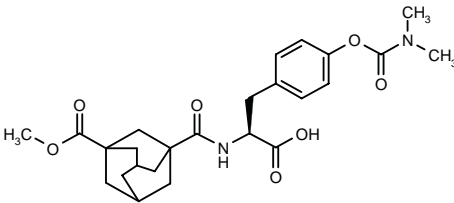
SOURCES – American Home Products; Elan.

REFERENCES

1. Dressen, D.B. et al. (Elan Pharmaceuticals, Inc.;American Home Products Corp.) *Pyroglutamic acid derivs. and related cpds. which inhibit leukocyte adhesion mediated by VLA-4*. WO 0043413.

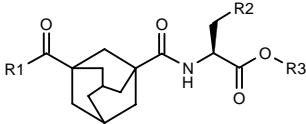
292934

N-[3-(Methoxycarbonyl)adamant-1-ylcarbonyl]-4-*O*-(*N,N*-dimethylcarbamoyl)-L-tyrosine



C25 H32 N2 O7; Mol wt: 472.5348

ACTION – Inhibitor of VLA-4-mediated leukocyte adhesion, potentially useful for the treatment of inflammatory diseases such as asthma, Alzheimer’s disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis and myocardial ischemia. Other exemplified multicyclic compounds include the following:



Compound	R1	R2	R3	Formula
292935	OH	4-[N(Me)2COO]-Ph	H	C ₂₄ H ₃₀ N ₂ O ₇
292936	OMe	4-(4-Me-1-Piz-COO)-Ph	H	C ₂₈ H ₃₇ N ₃ O ₇
292937	OMe	4-[1,3-(Me)2-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl]-Ph	H	C ₂₈ H ₃₃ N ₃ O ₇
292938	OMe	1-Pip	Me	C ₂₂ H ₃₄ N ₂ O ₅
292939	OMe	ethynyl-CON(Me)2	H	C ₂₁ H ₂₈ N ₂ O ₆
292941	Me	4-[N(Me)2COO]-Ph	i-Pr	C ₂₈ H ₃₈ N ₂ O ₆
292942	OMe	2-Pyr	Me	C ₂₂ H ₂₈ N ₂ O ₅

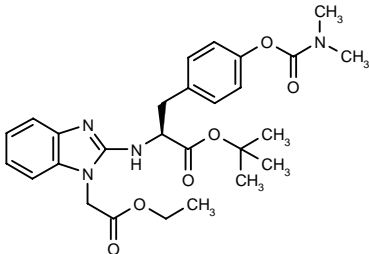
SOURCE – Elan.

REFERENCES

1. Grant, F.S. et al. (Elan Pharmaceuticals, Inc.) *Multicyclic opds. which inhibit leukocyte adhesion mediated by VLA-4.* WO 0043354.

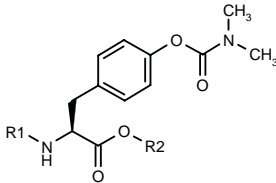
292958

N-[1-(Ethoxycarbonylmethyl)-1*H*-benzimidazol-2-yl]-4-*O*-(*N,N*-dimethylcarbamoyl)-L-tyrosine *tert*-butyl ester



C27 H34 N4 O6; Mol wt: 510.5876

ACTION – Inhibitor of VLA-4-mediated leukocyte adhesion, potentially useful for the treatment of inflammatory diseases such as asthma, Alzheimer’s disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis and myocardial ischemia. Other specifically claimed fused ring heteroaryl and heterocyclic compounds are:



Compound	R1	R2	Formula
292961	1-(EtOCOCH2)--2-benzimidazolyl	H	C ₂₃ H ₂₆ N ₄ O ₆
292962	2-benzoxazolyl	t-Bu	C ₂₃ H ₂₇ N ₃ O ₅
292963	2-benzoxazolyl	H	C ₁₉ H ₁₉ N ₃ O ₅
292964	2-benzothiazolyl	t-Bu	C ₂₃ H ₂₇ N ₃ O ₄ S
292966	2-benzothiazolyl	H	C ₁₉ H ₁₉ N ₃ O ₄ S
292969	2-cyclohexyl-4-quinazoliny	t-Bu	C ₃₀ H ₃₈ N ₄ O ₄
292970	2-cyclohexyl-4-quinazoliny	H	C ₂₆ H ₃₀ N ₄ O ₄
292971	2-(1-Pip)-4-quinazoliny	t-Bu	C ₂₉ H ₃₇ N ₅ O ₄
292972	2-(1-Pip)-4-quinazoliny	H	C ₂₅ H ₂₉ N ₅ O ₄

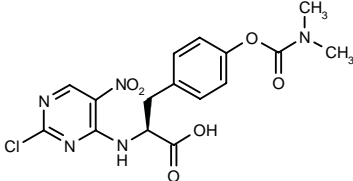
SOURCE – Elan.

REFERENCES

1. Grant, F.S. et al. (Elan Pharmaceuticals, Inc.) *Fused ring heteroaryl and heterocyclic opds. which inhibit leukocyte adhesion mediated by VLA-4.* WO 0043371.

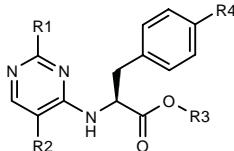
292973

N-(2-Chloro-5-nitropyrimidin-4-yl)-4-*O*-(*N,N*-dimethylcarbamoyl)-L-tyrosine

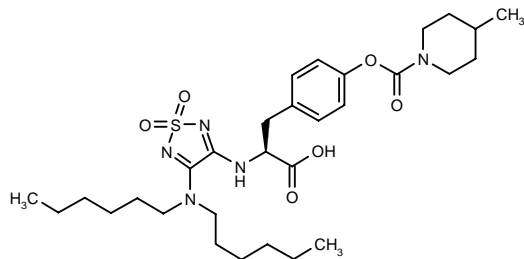


C16 H16 Cl N5 O6; Mol wt: 409.7844

ACTION – Inhibitor of VLA-4-mediated leukocyte adhesion, potentially useful for the treatment of inflammatory diseases such as asthma, Alzheimer’s disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis and myocardial ischemia. Other specifically claimed acyl derivatives include the following:



Compound	R1	R2	R3	R4	Formula
292974	1-Me-4-Pip-N(Me)	2-Me-Ph	H	OCON(Me)2	C ₃₀ H ₃₈ N ₆ O ₄
292975	H	3-Pyr-SO2N(Me)	i-Pr	4-Me-1-Pip-COO	C ₂₉ H ₃₆ N ₆ O ₆ S
292976	H	1-Pip	H	OCON(Me)2	C ₂₁ H ₂₇ N ₆ O ₄
292977	cyclohexyl-N(Me)	3-Pyr	H	OCON(Me)2	C ₂₈ H ₃₄ N ₆ O ₄
292978	cyclohexyl-N(Me)	2-thienyl	H	4-CF3-Ph	C ₃₁ H ₃₁ F ₃ N ₄ O ₂ S
292979	H	i-PrN(Me)	H	OCON(Me)2	C ₂₀ H ₂₇ N ₆ O ₄



292980:C30 H47 N5 O6 S

SOURCES – American Home Products; Elan.

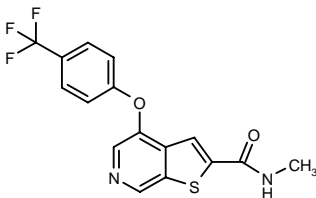
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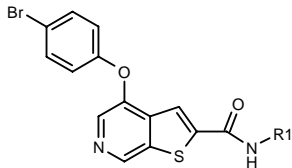
292653

N-Methyl-4-[4-(trifluoromethyl)phenoxy]thieno[2,3-c]-pyridine-2-carboxamide



C16 H11 F3 N2 O2 S; Mol wt: 352.3349

ACTION – Cell adhesion inhibitor that selectively inhibits ICAM-1 and E-selectin (IC₅₀ = 1 and 0.7 nM, respectively, against TNF-α-induced ICAM-1 and E-selectin expression in human umbilical vein endothelial cells), but not VCAM-1 expression (IC₅₀ > 1 μM). Compound exhibited a favorable oral pharmacokinetic profile in rats, giving a C_{max} of 2.53 μg/ml and a t_{1/2} of 3.7 h after dosing with 25 mg/kg. It was effective in rats with rheumatoid arthritis and in a mouse asthma model, where at a dose of 30 mg/kg it reduced eosinophil influx and ICAM-1 levels in both serum and bronchoalveolar lavage. Potentially useful for the treatment of inflammatory diseases including bronchial asthma. Other compounds from this series of 4-aryloxy-thieno[2,3-c]pyridines are:



Compound	R1	Formula
A-277232 [292654]	Me	C ₁₆ H ₁₁ BrN ₂ O ₂ S
A-249377 [292655]	H	C ₁₄ H ₉ BrN ₂ O ₂ S

SOURCES – Abbott; ICOS.

REFERENCES

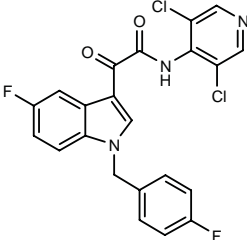
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2. Zhu, G.-D. et al. *Selective inhibition of ICAM-1 and E-selectin expression in human endothelial cells: Aryl modification of 4-aryloxy thieno[2,3-C]pyridines*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 145.

AWD-12-343

290744

N-(3,5-Dichloropyridin-4-yl)-2-[5-fluoro-1-(4-fluorobenzyl)-1H-indol-3-yl]-2-oxoacetamide



C22 H13 Cl2 F2 N3 O2; Mol wt: 460.2657

ACTION – Orally active, potent phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 9 nM) with high selectivity relative to other phosphodiesterases (IC₅₀ > 1 μM against PDE3, PDE5 and PDE7) and low affinity for the rolipram binding site (IC₅₀ = 313 nM). Compound inhibited the *in vitro* release of proinflammatory mediators such as TNF-α and GM-CSF from allergically challenged human nasal polyp cells with IC₅₀ values of 0.22 and 0.26 μM, respectively. *In vivo*, compound was seen to inhibit lipopolysaccharide-induced lung neutrophilia in rats with potency superior to that of rolipram (90 and 61% inhibition, respectively, at the dose of 1 mg/kg p.o.). Selected for further investigation as a therapeutic agent for the treatment of inflammatory diseases such as asthma and chronic obstructive pulmonary disease (COPD).

SOURCE – Asta Medica.

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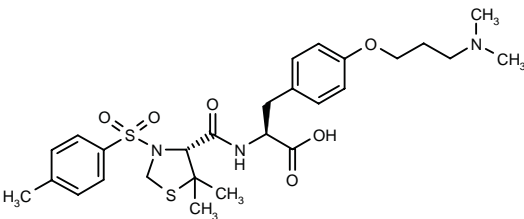
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CT-747^{1,3,4}

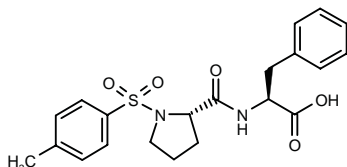
292391

N-[5,5-Dimethyl-3-(4-methylphenylsulfonyl)thiazolidin-4(R)-ylcarbonyl]-4-O-[3-(dimethylamino)propyl]-L-tyrosine



C27 H37 N3 O6 S2; Mol wt: 563.7363

ACTION – Potent and highly selective small-molecule VLA-4 inhibitor (IC_{50} = 0.4 nM for inhibition of the interaction between soluble VCAM-1 and Jurkat cells) proven to inhibit Jurkat cell adhesion to TNF- α -stimulated rat brain endothelial cells (IC_{50} = 0.2-1 μ M). Compound is a non-natural proline analogue of the potent VLA-4 inhibitor **CT-757** with an improved pharmacokinetic profile, with a $t_{1/2}$ of 1.5 h and an AUC of 4.7 μ g.h/ml in rats given a dose of 10 mg/kg i.v. Potentially useful for the treatment of inflammatory diseases including asthma.



CT-757 [292390]:^{2,5} C₂₁ H₂₄ N₂ O₅ S

SOURCES – Elan; Wyeth-Ayerst.

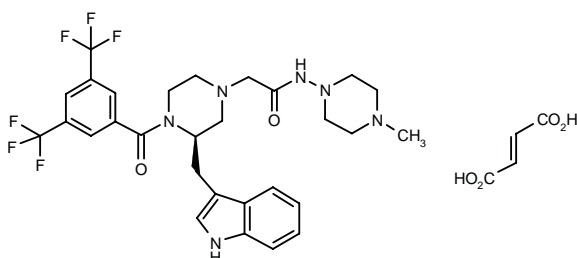
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5. Semko, C.M. et al. *Development of CT 757: A potent and highly selective small molecule inhibitor of VLA4*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 133.

FK-355*

245825

2-[4-[3,5-Bis(trifluoromethyl)benzoyl]-3(*R*)-(1*H*-indol-3-ylmethyl)piperazin-1-yl]-*N*-(4-methylpiperazin-1-yl)acetamide fumarate



C₂₉ H₃₂ F₆ N₆ O₂ . C₄ H₄ O₄; Mol wt: 726.6714

ACTION – Nonpeptide neurokinin NK₁ receptor antagonist with nanomolar affinity for NK₁ receptors in guinea pig lung and rat brain (IC_{50} = 8.9 and 22 nM, respectively). It exhibited potent inhibitory activity against substance P-induced airways edema in guinea pigs (ED_{50} = 0.011 and 0.074 mg/kg i.v. and p.o., respectively). Potentially useful for the treatment of respiratory diseases including asthma.

SOURCE – Fujisawa.

REFERENCES

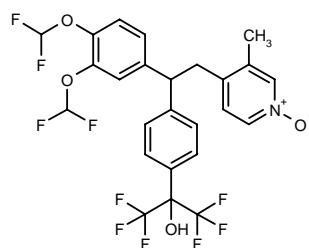
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2. Manabe, T. et al. *Design and synthesis of new non-peptide NK1 antagonists by chemical modification of FK888*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 121.

*Identified compound **245825** Drug Data Rep 1997, 019(04): 0298.

L-826141¹⁻⁴

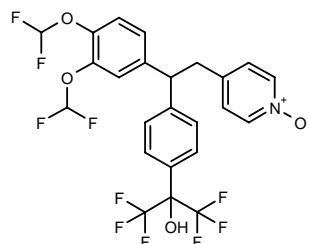
293604

4-[2-[3,4-Bis(difluoromethoxy)phenyl]-2-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethyl]-3-methylpyridine *N*-oxide



C₂₅ H₁₉ F₁₀ N O₄; Mol wt: 587.4081

ACTION – Potent phosphodiesterase type 4 (PDE4) inhibitor (IC_{50} = 0.3 nM against the human PDE4A isoform and IC_{50} = 0.2 μ M for inhibition of lipopolysaccharide-stimulated TNF- α production in human whole blood) emerging from SAR studies conducted to optimize pharmacokinetic behavior of the potent PDE4 inhibitor **L-791943**. Compound showed an improved pharmacokinetic profile in rats, dogs and monkeys after i.v. administration, with a shorter half-life (10 h versus > 24 h for L-791943). *In vivo*, compound was seen to inhibit bronchoconstriction induced by ovalbumin in guinea pigs (82% inhibition at 1 mg/kg i.p.) and by *Ascaris* antigen in conscious sheep (62 and 91% inhibition of early and late phase, respectively, at 2 mg/kg i.v.). In addition, compound was orally active in a squirrel monkey model of antigen-induced bronchoconstriction, with 26-59 and 38-100% inhibition of the early- and late-phase responses at doses of 0.5-3 mg/kg. Compound was not emetic in ferrets up to the dose of 30 mg/kg p.o. Potentially useful for the treatment of chronic inflammatory diseases such as asthma and chronic obstructive pulmonary disease (COPD).



L-791943 [293603]¹⁻³: C₂₄ H₁₇ F₁₀ N O₄

SOURCE – Merck Frosst.

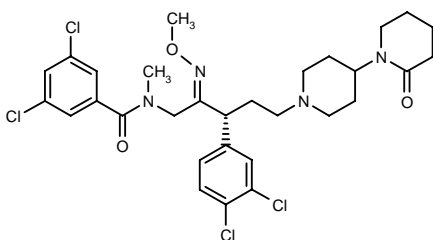
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SCH-205528

292388

N-[3(*R*)-(3,4-Dichlorophenyl)-5-[4-(2-oxopiperidin-1-yl)piperidin-1-yl]-2(*Z*)-(methoxyimino)pentyl]-*N*-methyl-3,5-dichlorobenzamide



C30 H36 Cl4 N4 O3; Mol wt: 642.4514

ACTION – Dual tachykinin NK₁ and NK₂ receptor antagonist with K_i values of 1 and 0.7 nM, respectively, in binding assays. Compound showed antagonist activity in *in vitro* functional assays and *in vivo* models. Potentially useful for the treatment of asthma, allergic rhinitis and related disorders.

SOURCE – Schering-Plough.

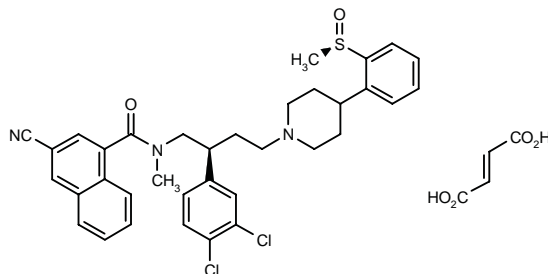
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ZD-6021

292841

3-Cyano-*N*-[2(*S*)-(3,4-dichlorophenyl)-4-[4-[2-[(*R*)-methylsulfinyl]phenyl]piperidin-1-yl]butyl]-*N*-methyl-naphthalene-1-carboxamide fumarate



C35 H35 Cl2 N3 O2 S . C4 H4 O4; Mol wt: 748.7241

ACTION – High-affinity ligand for human neurokinin NK₁ and NK₂ receptors (K_i = 0.12 and 0.64 nM, respectively) with lower affinity for the NK₃ receptor (K_i = 74 nM) and functional antagonist activity against NK₁ and NK₂ receptors in rabbit pulmonary artery (pA₂ = 8.7 and 8.5, respectively) and human pulmonary artery and bronchus preparations (pK_B = 8.9 and 7.5, respectively). In guinea pigs, compound given orally antagonized NK₁ agonist-induced tracheal plasma protein extravasation (ED₅₀ = 0.8 μmol/kg), as well as NK₂ agonist-induced bronchoconstriction (ED₅₀ = 20 μmol/kg). Potentially useful for the treatment of tachykinin-related diseases including bronchial asthma and inflammation.

SOURCE – AstraZeneca.

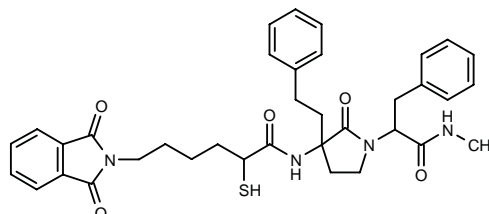
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2. Rumsey, W.L. et al. *Pharmacological characterization of a novel, orally active tachykinin antagonist, ZD6021*. Eur Respir J 2000, 16(Suppl. 31): Abst P3956.

AGENTS FOR ARDS AND EMPHYSEMA

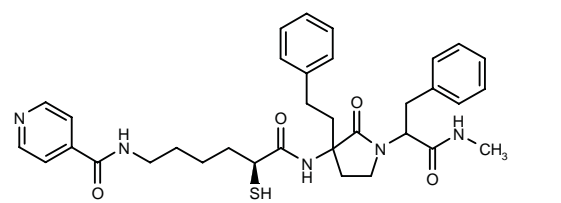
292358

N-[1-[1-Benzyl-2-(methylamino)-2-oxoethyl]-2-oxo-3-(2-phenylethyl)pyrrolidin-3-yl]-6-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-2-sulfanylhexasanamide

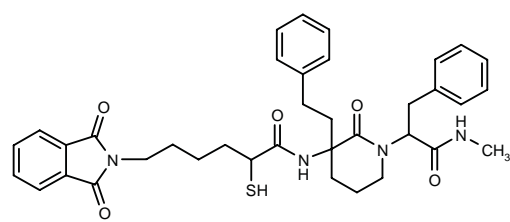


C36 H40 N4 O5 S; Mol wt: 640.8010

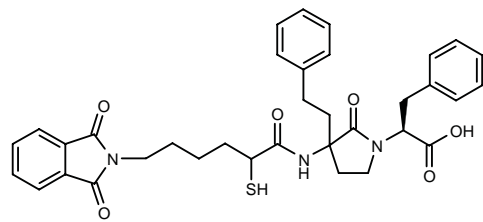
ACTION – Matrix metalloproteinase inhibitor expected to be useful for the treatment of neoplastic diseases and chronic inflammatory disorders such as emphysema. Other specifically claimed 3-(thio-substituted amido)-lactams are:



292359: C34 H41 N5 O4 S



292360: C37 H42 N4 O5 S



292361: C35 H37 N3 O6 S

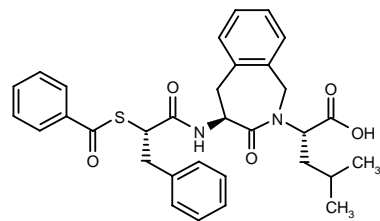
SOURCE – Aventis Pharma.

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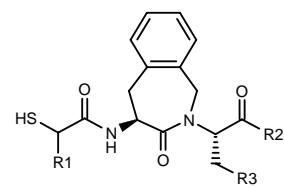
292362

2-(S)-[4(S)-[2(S)-(Benzoylsulfanyl)-3-phenylpropion-amido]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepin-2-yl]-4-methylpentanoic acid



C32 H34 N2 O5 S; Mol wt: 558.6956

ACTION – Matrix metalloproteinase inhibitor expected to be useful for the treatment of neoplastic diseases, atherosclerosis and chronic inflammatory disorders such as emphysema, and especially smoking-induced emphysema. Other exemplified *N*-carboxymethyl substituted benzolactams are:



Compound	R1	R2	R3	Formula
292363	(S)-CH2Ph	OH	i-Pr	C ₂₅ H ₃₀ N ₂ O ₄ S
292364	1,3-dioxo-2-isoindoliny-(CH2)4	OH	i-Pr	C ₃₀ H ₃₅ N ₃ O ₆ S
292365	1,3-dioxo-2-isoindoliny-(CH2)4	NHMe	Ph	C ₃₄ H ₃₆ N ₄ O ₅ S

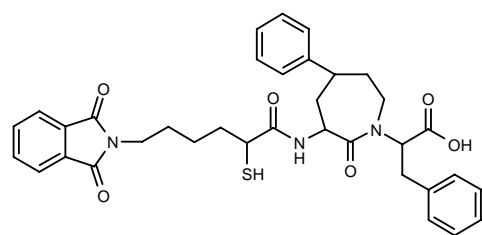
SOURCE – Aventis Pharma.

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1. Warshawsky, A. et al. (Aventis Pharmaceuticals, Inc.) *N-Carboxymethyl substd. benzolactams as inhibitors of matrix metalloproteinase*. WO 0040564.

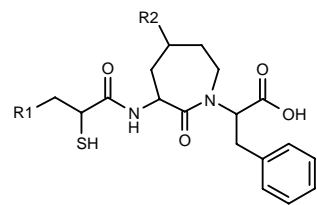
292373

2-[3-[6-(1,3-Dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-2-sulfanylhexanamido]-2-oxo-5-phenylperhydroazepin-1-yl]-3-phenylpropionic acid



C35 H37 N3 O6 S; Mol wt: 627.7583

ACTION – Selective inhibitor of the matrix metallo-proteinase MMP-12 (metalloelastase), particularly useful for the treatment of smoking-induced emphysema. The compound is expected to be of use for long-term therapy, with reduced side effects compared to broad-spectrum inhibitors. Other exemplified 1-carboxymethyl-2-oxo-azepan derivatives are:



Compound	R1	R2	Formula
292374	1,3-dioxo-2-isoindoliny-(CH2)3	Me	C ₃₀ H ₃₅ N ₃ O ₆ S
292375	Ph	Ph	C ₃₀ H ₃₂ N ₂ O ₄ S

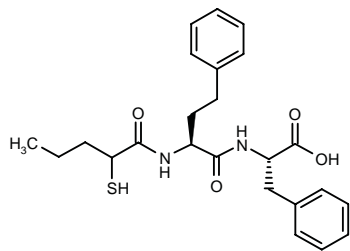
SOURCE – Aventis Pharma.

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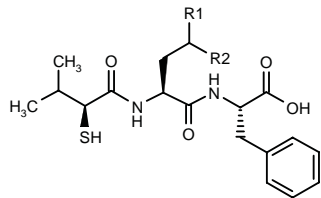
292376

N-[4-Phenyl-2(*S*)-(2-sulfanylpentanamido)butyryl]-L-phenylalanine



C24 H30 N2 O4 S; Mol wt: 442.5770

ACTION – Selective inhibitor of the matrix metalloproteinase MMP-12 (metalloelastase), giving K_i values for inhibition of MMP-1 (fibroblast collagenase), MMP-2 (gelatinase A), MMP-3 (stromelysin 1) and MMP-12 of 5800, 1800, 750 and 13 nM, respectively. The compound is particularly useful for the treatment of smoking-induced emphysema, allowing long-term therapy with reduced side effects associated with broad-spectrum inhibitors. Other exemplified mercaptoacetylamido dipeptide carboxylic acids are:



Compound	R1	R2	Formula
292377	H	Ph	C ₂₄ H ₃₀ N ₂ O ₄ S
292378	Me	Me	C ₂₀ H ₃₀ N ₂ O ₄ S
292379	H	SMe	C ₁₉ H ₂₈ N ₂ O ₄ S ₂
292380	H	CH ₂ CH ₂ NH ₂	C ₂₀ H ₃₁ N ₃ O ₄ S

SOURCE – Aventis Pharma.

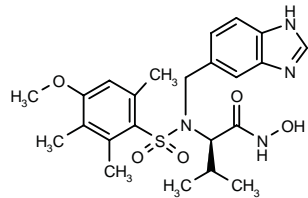
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TREATMENT OF CYSTIC FIBROSIS

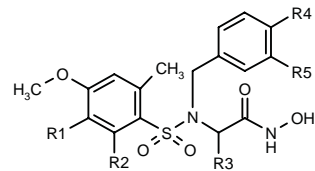
291982

2(*R*)-[*N*-(1*H*-Benzimidazol-5-ylmethyl)-*N*-(4-methoxy-2,3,6-trimethylphenylsulfonyl)amino]-3-methylbutyrohydroxamic acid



C23 H30 N4 O5 S; Mol wt: 474.5790

ACTION – Inhibitor of procollagen C-proteinase (procollagen C-endopeptidase), the enzyme that catalyzes the cleavage of the C-propeptide of types I, II and III collagens and is essential in the formation of functional collagen fibers. It is therefore potentially useful in the treatment of diseases mediated by excessive collagen deposition such as interstitial pulmonary fibrosis, pericentral fibrosis, Symmers' fibrosis, perimuscular fibrosis, kidney and liver fibrosis, idiopathic pulmonary fibrosis, endocardial sclerosis, hepatitis, ARDS, arthritis, cystic fibrosis, tendon surgery, surgical adhesions, corneal scarring and restenosis. Other exemplified sulfonamide hydroxamates include the following:



Compound	R1	R2	R3	R4	R5	Formula
291983	Me	Me	(<i>R</i>)- <i>i</i> -Pr	-OCH ₂ O-		C ₂₃ H ₃₀ N ₂ O ₇ S
291984	Me	Me	(<i>R</i>)-CH ₂ OH	-OCH ₂ O-		C ₂₁ H ₂₈ N ₂ O ₈ S
291985	Me	Me	(<i>R</i>)- <i>t</i> -BuOCH ₂	-NHCH=CH-		C ₂₆ H ₃₆ N ₃ O ₆ S
291986	Me	H	(<i>R</i>)- <i>i</i> -Pr	-NHCH=CH-		C ₂₃ H ₂₉ N ₃ O ₅ S
291987	H	Me	(<i>R</i>)- <i>i</i> -Pr	-OCH ₂ O-		C ₂₂ H ₂₈ N ₂ O ₇ S
291988	Me	Me	(<i>R</i>)- <i>i</i> -Pr	-NHCH=C(Ac)-		C ₂₆ H ₃₃ N ₃ O ₆ S
291989	H	Me	(<i>R</i>)-CH ₂ SO ₂ NHMe	-OCH ₂ O-		C ₂₁ H ₂₇ N ₃ O ₉ S ₂
291990	Me	Me	(<i>R</i>)-CH ₂ CO ₂ Me	-OCH ₂ O-		C ₂₃ H ₂₈ N ₂ O ₉ S

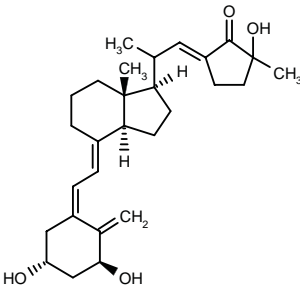
SOURCE – Roche.

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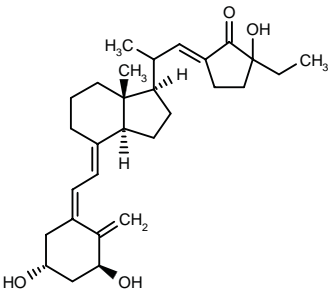
292316

1 α -Hydroxy-22-(3-hydroxy-3-methyl-2-oxocyclopentylidene)-23,24,25,26,27-pentanorvitamin D₃



C28 H40 O4; Mol wt: 440.6200

ACTION – Vitamin D₃ derivative for the treatment of cystic fibrosis, with reduced calcemic activity as compared with calcitriol. Another exemplified compound is:



292317: C29 H42 O4

SOURCE – Teijin.

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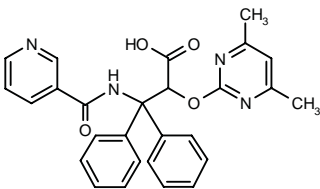
1. Takenouchi, K. et al. (Teijin Ltd.) *Cystic fibrosis remedies containing vitamin D₃ derivs.* WO 0038692.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

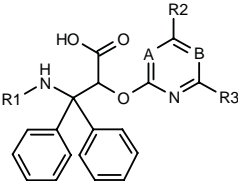
291878

2-(4,6-Dimethylpyrimidin-2-yloxy)-3,3-diphenyl-3-(3-pyridinylcarboxamido)propionic acid



C27 H24 N4 O4; Mol wt: 468.5106

ACTION – Endothelin receptor antagonist with high affinity and selectivity for the ET_A receptor, giving a K_i of 52 nM versus 6700 nM for the ET_B receptor. Potentially useful for the treatment of hypertension, chronic heart failure, restenosis, pulmonary hypertension, acute and chronic renal disease, erectile dysfunction, cerebral ischemia, benign prostatic hyperplasia and prostate cancer. Other compounds from this series of β -amide and β -sulfonamide carboxylic acid derivatives are:



Compound	R1	R2	R3	A	B	Formula
291879	4-MeO-PhCO	Et	Et	N	N	C ₃₀ H ₃₀ N ₄ O ₅
291880	3,4-(MeO)2-PhCO	Me	Me	N	CH	C ₃₀ H ₂₉ N ₃ O ₆
291881	COPh	Me	Me	N	CH	C ₂₈ H ₂₅ N ₃ O ₄
291882	SO2Me	OMe	OMe	N	CH	C ₂₂ H ₂₃ N ₃ O ₇ S
291883	4-F-PhCO	Me	Me	N	CH	C ₂₈ H ₂₄ FN ₃ O ₄
291884	4-Me-PhCO	Me	Me	N	CH	C ₂₉ H ₂₇ N ₃ O ₄
291885	4-CF3-PhCO	OMe	Me	CH	N	C ₂₉ H ₂₄ F ₃ N ₃ O ₅
291886	3,5-(MeO)2-PhCO	Me	Me	N	CH	C ₃₀ H ₂₉ N ₃ O ₆
291887	3,4-(F)2-PhCO	Me	Me	N	CH	C ₂₈ H ₂₃ F ₂ N ₃ O ₄

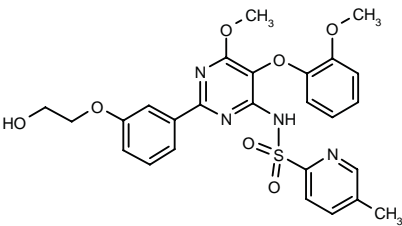
SOURCE – BASF.

REFERENCES

1. Amberg, W. et al. (BASF AG) *New β -amide and β -sulfonamide carboxylic acid derivs., their production and their use as endothelin receptor antagonists.* DE 19858779, WO 0037450.

292532

N-[2-[3-(2-Hydroxyethoxy)phenyl]-6-methoxy-5-(2-methoxyphenyl)pyrimidin-4-yl]-5-methylpyridine-2-sulfonamide

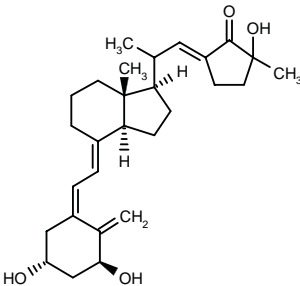


C26 H26 N4 O7 S; Mol wt: 538.5784

ACTION – Endothelin receptor antagonist found to inhibit endothelin binding in CHO cells expressing recombinant human ET_A receptors (IC₅₀ = 10 nM or less) and endothelin-induced contractions in isolated rat aorta rings (pA₂ = 8.2 or more). When administered to rats at 5 mg/kg p.o. by gavage, a peak plasma concentration of 1500 ng/ml or higher and an AUC of 10,000 ng.h/ml or greater were determined. Other exemplified 4-(heterocyclysulfonamido)-5-methoxy-6-(2-methoxyphenoxy)-2-(phenyl or pyridyl)pyrimidines include the following:

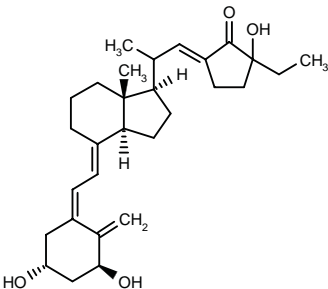
292316

1 α -Hydroxy-22-(3-hydroxy-3-methyl-2-oxocyclopentylidene)-23,24,25,26,27-pentanorvitamin D₃



C28 H40 O4; Mol wt: 440.6200

ACTION – Vitamin D₃ derivative for the treatment of cystic fibrosis, with reduced calcemic activity as compared with calcitriol. Another exemplified compound is:



292317: C29 H42 O4

SOURCE – Teijin.

REFERENCES

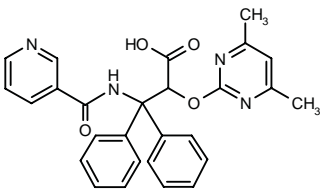
1. Takenouchi, K. et al. (Teijin Ltd.) *Cystic fibrosis remedies containing vitamin D₃ derivs.* WO 0038692.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

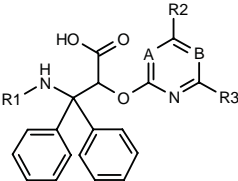
291878

2-(4,6-Dimethylpyrimidin-2-yloxy)-3,3-diphenyl-3-(3-pyridinylcarboxamido)propionic acid



C27 H24 N4 O4; Mol wt: 468.5106

ACTION – Endothelin receptor antagonist with high affinity and selectivity for the ET_A receptor, giving a K_i of 52 nM versus 6700 nM for the ET_B receptor. Potentially useful for the treatment of hypertension, chronic heart failure, restenosis, pulmonary hypertension, acute and chronic renal disease, erectile dysfunction, cerebral ischemia, benign prostatic hyperplasia and prostate cancer. Other compounds from this series of β -amide and β -sulfonamide carboxylic acid derivatives are:



Compound	R1	R2	R3	A	B	Formula
291879	4-MeO-PhCO	Et	Et	N	N	C ₃₀ H ₃₀ N ₄ O ₅
291880	3,4-(MeO)2-PhCO	Me	Me	N	CH	C ₃₀ H ₂₉ N ₃ O ₆
291881	COPh	Me	Me	N	CH	C ₂₈ H ₂₅ N ₃ O ₄
291882	SO2Me	OMe	OMe	N	CH	C ₂₂ H ₂₃ N ₃ O ₇ S
291883	4-F-PhCO	Me	Me	N	CH	C ₂₈ H ₂₄ FN ₃ O ₄
291884	4-Me-PhCO	Me	Me	N	CH	C ₂₉ H ₂₇ N ₃ O ₄
291885	4-CF3-PhCO	OMe	Me	CH	N	C ₂₉ H ₂₄ F ₃ N ₃ O ₅
291886	3,5-(MeO)2-PhCO	Me	Me	N	CH	C ₃₀ H ₂₉ N ₃ O ₆
291887	3,4-(F)2-PhCO	Me	Me	N	CH	C ₂₈ H ₂₃ F ₂ N ₃ O ₄

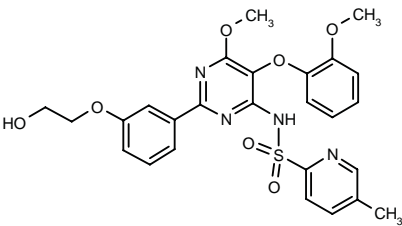
SOURCE – BASF.

REFERENCES

1. Amberg, W. et al. (BASF AG) *New β -amide and β -sulfonamide carboxylic acid derivs., their production and their use as endothelin receptor antagonists.* DE 19858779, WO 0037450.

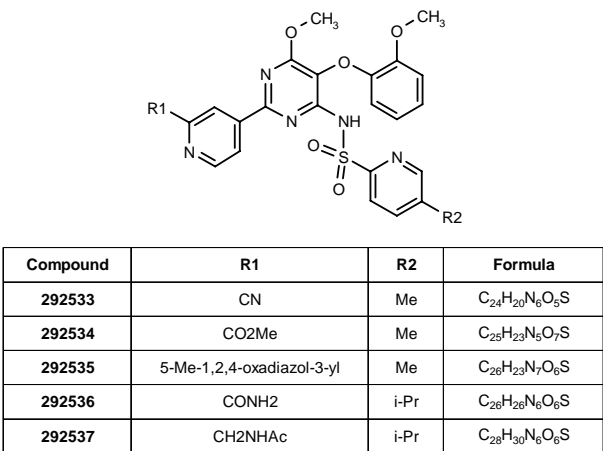
292532

N-[2-[3-(2-Hydroxyethoxy)phenyl]-6-methoxy-5-(2-methoxyphenyl)pyrimidin-4-yl]-5-methylpyridine-2-sulfonamide



C26 H26 N4 O7 S; Mol wt: 538.5784

ACTION – Endothelin receptor antagonist found to inhibit endothelin binding in CHO cells expressing recombinant human ET_A receptors (IC₅₀ = 10 nM or less) and endothelin-induced contractions in isolated rat aorta rings (pA₂ = 8.2 or more). When administered to rats at 5 mg/kg p.o. by gavage, a peak plasma concentration of 1500 ng/ml or higher and an AUC of 10,000 ng.h/ml or greater were determined. Other exemplified 4-(heterocyclysulfon-amido)-5-methoxy-6-(2-methoxyphenoxy)-2-(phenyl or pyridyl)pyrimidines include the following:



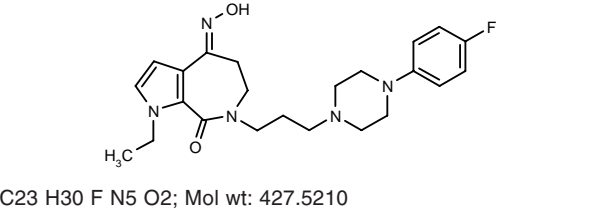
SOURCE – Roche.

REFERENCES

1. Breu, V. et al. (F. Hoffmann-La Roche AG) 4-(Heterocyclylsulfonamido)-5-methoxy-6-(2-methoxyphenoxy)-2-phenyl- or pyridylpyrimidines as endothelin receptor antagonists. WO 0042035.

292721

1-Ethyl-7-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1*H*,5*H*)-dione 4-oxime



ACTION – Antihypertensive agent with dual α_1 -adrenoceptor- and 5-HT₂ receptor-antagonist activity (pA_2 = 7.83 and 9.47, respectively, for antagonism of norepinephrine- and 5-HT-induced contractions in isolated guinea pig arteries). In DOCA-salt hypertensive dogs, compound at a dose of 3 mg/kg p.o. showed potent and long-lasting blood pressure-lowering activity (at least 20% reduction for over 4 h), being more potent than doxazosin. In addition, at doses of 0.3 mg/kg p.o. or above it protected mice against pulmonary thromboembolic death due to collagen + 5-HT-induced platelet aggregation, mortality being only 20% even at 6 h after 3 mg/kg.

SOURCE – Suntory.

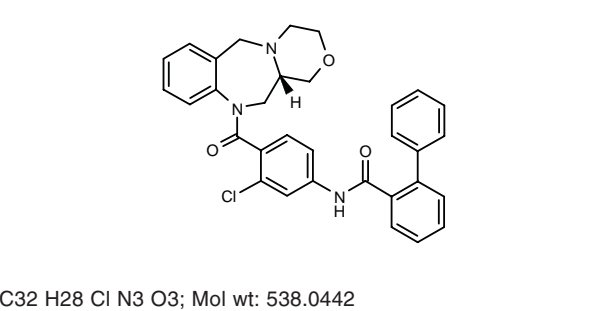
REFERENCES

1. Mizuno, A. et al. (Suntory Ltd.) *Pyrroloazepine cpd.* EP 0557526, JP 1993503481, US 5399557, WO 9303032.

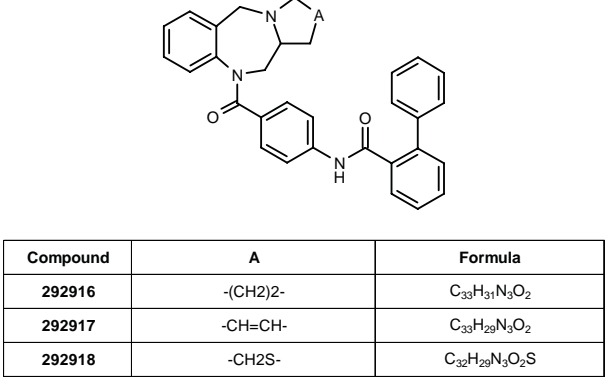
2. Mizuno, A. et al. *Studies on antihypertensive agents with antithrombotic activity. 2. Syntheses and pharmacological evaluation of pyrrolo[2,3-c]azepine derivatives.* Chem Pharm Bull 2000, 48(8): 1129.

292915

N-[4-[(12*aS*)-3,4,6,11,12,12*a*-Hexahydro-1*H*-[1,4]-oxazino[3,4-*c*][1,4]benzodiazepin-11-ylcarbonyl]-3-chlorophenyl]biphenyl-2-carboxamide



ACTION – Vasopressin receptor antagonist with the ability to displace [³H]-arginine vasopressin binding from human V₁ and V₂ receptors in HEK-293 cells and to reverse [³H]-arginine vasopressin-induced hypertension in anesthetized rats, producing a 100% reduction in blood pressure at 10 mg/kg i.d. Potentially useful for the treatment of disorders involving increased vascular resistance, particularly hypertension, congestive heart failure, cardiac insufficiency, coronary vasospasm, cardiac ischemia, liver cirrhosis, renal vasospasm, renal failure, cerebral edema and ischemia, stroke, thrombosis and water retention. Other exemplified tricyclic benzodiazepines include the following:



SOURCE – Ortho-McNeil.

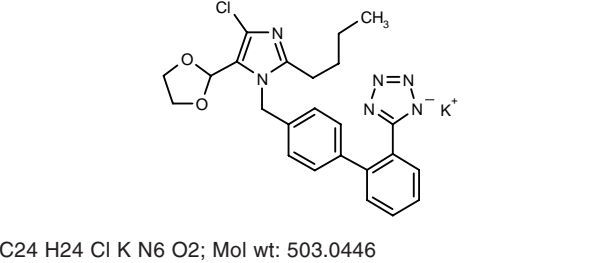
REFERENCES

1. Hoekstra, W.J. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Tricyclic benzodiazepines as vasopressin receptor antagonists.* WO 0043398.

FI-6828K*

290474

5-[4'-[2-Butyl-4-chloro-5-(1,3-dioxolan-2-yl)-1*H*-imidazol-1-ylmethyl]biphenyl-2-yl]-1*H*-tetrazole potassium salt



ACTION – Angiotensin AT₁ receptor antagonist with antihypertensive activity in three preclinical models in rats. In furosemide-treated rats and spontaneously hypertensive rats, doses of 3-30 mg/kg p.o. were associated with a reduction in mean arterial pressure (MAP) of 21-27 mmHg, with a more rapid onset than losartan and a maximum effect at 5-6 h. In renal hypertensive rats, compound reduced MAP by 26-62 mmHg at doses ranging from 1 to 30 mg/kg p.o., with superior efficacy compared to losartan. Selected as a candidate for development for the treatment of hypertension.

SOURCE – Ferrer.

REFERENCES

1. Foguet, R. et al. (Ferrer Internacional SA) *2-Alkyl-5-halo-3-[2'-(tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazole-4-carboxaldehyde acetal derivs., their preparation and use.* WO 0031071.

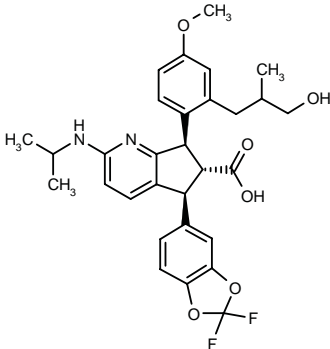
2. Terencio, J. et al. *Antihypertensive activity of FI-6828K, a new angiotensin II receptor blocker, in rat hypertensive models.* Methods Find Exp Clin Pharmacol 2000, 22(6): Abst P-9.

*Identified compound **290474** Drug Data Rep 2000, 022(09): 0789.

J-112287*

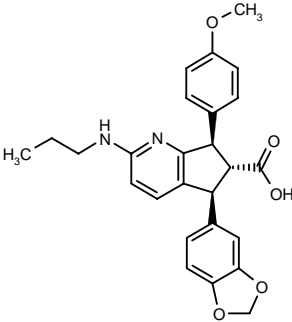
279590

5-(S)-(2,2-Difluoro-1,3-benzodioxol-5-yl)-7(R)-[2-(3-hydroxy-2-methylpropyl)-4-methoxyphenyl]-2-(isopropyl-amino)-6,7-dihydro-5H-cyclopenta[b]pyridine-6(R)-carboxylic acid



C30 H32 F2 N2 O6; Mol wt: 554.5868

ACTION – Potent, orally active and selective endothelin ET_A receptor antagonist with subnanomolar binding affinity for ET_A receptors (K_i = 0.066 nM) and 5,200-fold selectivity over ET_B receptors (K_i = 380 nM). Compound showed antagonist activity on isolated rabbit iliac artery (pA₂ = 9.7) and was able to prevent ET₁-induced death in mice (ED₅₀ = 0.13 mg/kg i.v.). Compound exhibited a strong antihypertensive effect in conscious Dahl salt-sensitive rats, giving a long-lasting decrease in mean blood pressure of about 30 mmHg at 6-7 h after treatment with the dose of 10 mg/kg p.o. Compound showed good oral bioavailability ranging from 28 to 40% in different species. Potentially useful for the management of hypertension. Another related cyclopentenopyridine derivative is:



J-105510 [293369]: C26 H26 N2 O5

SOURCE – Banyu.

REFERENCES

1. Hayama, T. et al. (Banyu Pharmaceutical Co., Ltd.) *Substd. 5-(2,2-difluoro-1,3-benzodioxol-5-yl) cyclopentenopyridine deriv.* WO 9937639.

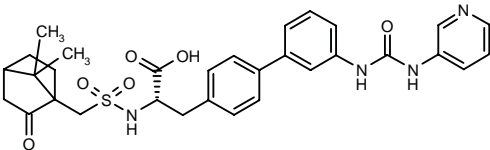
2. Hayama, T. et al. *New cyclopentenopyridine derivatives. A potent, orally active, selective endothelin ET_A receptor antagonist.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-78.

*Identified compound **279590** (see **279589**) Drug Data Rep 1999, 021(10): 0882.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

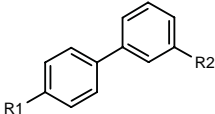
291677

N-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methylsulfonyl)-3-[3'-(3-(pyridin-3-yl)ureido)biphenyl-4-yl]-L-alanine

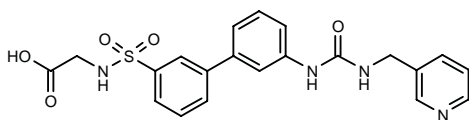


C31 H34 N4 O6 S; Mol wt: 590.6976

ACTION – Integrin antagonist, particularly active at the α_vβ₃ receptor (IC₅₀ = 2 nM in human A375 cells). It was also active in a smooth muscle cell migration test (IC₅₀ = 3-40 nM). Potentially useful for the treatment of osteoporosis, restenosis, cancer and atherosclerosis. Other exemplified biphenyl compounds are:



Compound	R1	R2	Formula
291678	2,4,6-(Me)3-Ph-SO2NHCH(CO2H)CH2	3-Pyr-CH2-NHCONH	C ₃₁ H ₃₂ N ₄ O ₅ S
291679	(S)-2,4,6-(Me)3-Ph-SO2NHCH(CO2H)CH2	cyclopropyl-NHCONH	C ₂₈ H ₃₁ N ₃ O ₅ S
291683	2,4,6-(Me)3-PhSO2-NHCH(CO2H)CH2	2-imidazolyl-NH	C ₂₇ H ₂₈ N ₄ O ₄ S
291684	SO2NHCH(Ph)-CH2CO2H	2-benzimidazolyl-CH2NHCH2	C ₃₀ H ₂₈ N ₄ O ₄ S
291685	(S)-2,4,6-(Me)3-Ph-SO2NHCH(CO2H)CH2	2-Pyr-NHCH2	C ₃₀ H ₃₁ N ₃ O ₄ S
291686	(S)-2,4,6-(Me)3-Ph-SO2NHCH(CO2H)CH2	2-imidazolyl-CONH	C ₂₈ H ₂₈ N ₄ O ₅ S



291682: C₂₁ H₂₀ N₄ O₅ S

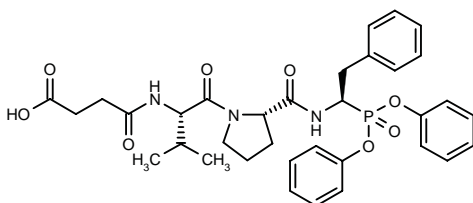
SOURCE – Bayer.

REFERENCES

1. Albers, M. et al. (Bayer AG) *New biphenyl and biphenyl-analogous cpds. as integrin antagonists*. WO 0035864.

292592

N-(3-Carboxypropanoyl)-L-valyl-*N*-[1(*S*)-(diphenoxyphosphinyl)-2-phenylethyl]-L-prolinamide



C₃₄ H₄₀ N₃ O₈ P; Mol wt: 649.6770

ACTION – Chymase inhibitor able to prevent vascular proliferation in dogs undergoing right carotid artery bypass grafting with the ipsilateral external jugular vein; compound infiltrated into the grafted vein at a concentration of 10 μM reduced the intimal area of grafted vein by 63.9% compared to controls. Potentially useful for the prevention of vascular diseases such as vascular proliferation in grafted vessels.

SOURCES – Dyax; Osaka Medical College, Osaka (JP).

REFERENCES

1. Powers, J.C. et al. (Georgia Technology Research Corp.) *Basic α-aminoalkylphosphonate derivs*. US 5952307.

2. Powers, J.C. et al. (Georgia Technology Research Corp.) *Proline phosphonate derivs*. WO 9529691.

3. Hof, P. et al. *The 1.8 Å crystal structure of human cathepsin G in complex with Suc-Val-Pro-PheP-(OPh)₂: A Janus-faced proteinase with two opposite specificities*. EMBO J 1996, 15(20): 5481.

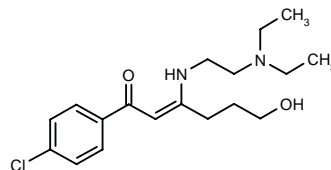
4. Oleksyszyn, J. and Powers, J.C. *Irreversible inhibition of serine proteases by peptide derivatives of (α-aminoalkyl) phosphonate diphenyl esters*. Biochemistry 1991, 30(2): 485.

5. Takai, S. et al. *Chymase inhibitor prevents vascular proliferation in dog grafted veins*. J Hypertens 2000, 18(Suppl. 4): Abst P4.45.

6. Takai, S. et al. *Inhibition of chymase reduces vascular proliferation in dog grafted veins*. FEBS Lett 2000, 467(2-3): 141.

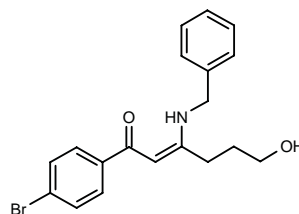
292878

1-(4-Chlorophenyl)-3-[2-(diethylaminoethyl)amino]-6-hydroxy-2(*Z*)-hexen-1-one



C₁₈ H₂₇ Cl N₂ O₂; Mol wt: 338.8763

ACTION – Hypolipidemic agent and antioxidant with a comparable activity profile but superior potency to probucol. Compound showed cholesterol-lowering activity in triton-treated rats (45% decrease at 100 mg/kg i.p.), significantly reduced the levels of lipids and apoproteins in hyperlipidemic rats at 50 mg/kg i.p., reactivated plasma lecithin cholesterol acyltransferase (LCAT) and partially restored the reduced HDL cholesterol. The antioxidant activity of the compound was measured as protection against Cu²⁺-mediated oxidation of LDL cholesterol (85% protection at 10 mM) and by its ability to scavenge superoxide anions and hydroxyl radicals *in vitro*. In addition, compound significantly reversed altered biochemical parameters such as CPK, alkaline phosphatase, GOT and GPT in rats with isoproterenol-induced cardiac ischemia. Potentially useful for the treatment of atherosclerosis. Another related compound is:



292877: C₁₉ H₂₀ Br N O₂

SOURCE – Central Drug Research Institute, Lucknow (IN).

REFERENCES

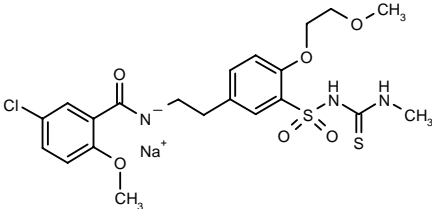
1. Batra, S. et al. *Syntheses and biological evaluation of 3-substituted amino-1-aryl-6-hydroxy-hex-2-ene-1-ones as antioxidant and hypolipidemic agents*. Bioorg Med Chem 2000, 8(8): 2195.

ANTIARRHYTHMIC DRUGS

HMR-1402

241812

5-Chloro-2-methoxy-*N*-[2-[4-(2-methoxyethoxy)-3-(3-methylthioureidosulfonyl)phenyl]ethyl]benzamide



C21 H25 Cl N3 O6 S2 . Na; Mol wt: 538.0185

ACTION – Cardiosensitive ATP-sensitive potassium (K_{ATP}) channel antagonist proven to be more potent than glibenclamide in inhibiting rilmakalim-induced shortening of the APD_{90} in guinea pig papillary muscle (IC_{50} = 98 and 140 nM, respectively). In dogs with healed myocardial infarction subjected to coronary occlusion during exercise, both compound (3.0 mg/kg i.v., 4 μ g/kg/min for 1 h prior to exercise) and glibenclamide (1.0 mg/kg i.v.) prevented ventricular fibrillation in almost all animals. However, unlike glibenclamide, compound was not associated with effects on coronary blood flow, plasma insulin or blood glucose. Potentially useful as an antiarrhythmic agent.

SOURCE – Aventis Pharma.

REFERENCES

1. Englert, H.C. et al. (Aventis SA) *Substd. benzenesulfonylureas and -thiureas, process for their preparation, their use as medicament or diagnostic agent, as well as medicaments containing them.* DE 19505397, EP 0727416, JP 1996245554, US 5652268.

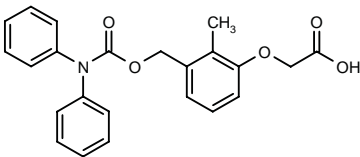
2. Billman, G.E. et al. *HMR 1402, a novel cardiosensitive ATP-sensitive potassium channel antagonist, prevents ventricular fibrillation induced by myocardial ischemia.* Circulation 2000, 102(18, Suppl.): Abst 1012.

3. Billman, G.E. et al. *HMR 1402, a novel cardiosensitive ATP-sensitive potassium channel antagonist, protects against ischaemically-induced ventricular fibrillation.* Eur Heart J 2000, 21(Suppl.): Abst P1766.

TREATMENT OF PERIPHERAL VASCULAR DISEASE

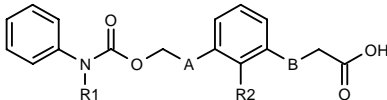
291945

2-[3-(*N,N*-Diphenylcarbamoyloxymethyl)-2-methylphenoxy]acetic acid



C23 H21 N O5; Mol wt: 391.4209

ACTION – Prostaglandin I_2 (IP) receptor agonist, potentially useful for accelerating wound healing and for the treatment of tissue necrosis, premature uterine contractions, gastric ulcer, sexual dysfunction, severe menstrual pain and disorders related to inadequate immunoregulation, platelet aggregation and neutrophil function. Preferably, the compound may be of use for the treatment of cardiovascular disorders including peripheral arterial occlusive disease, intermittent claudication, atherosclerosis, coronary artery disease, stroke, etc. Other specifically claimed compounds are:



Compound	R1	R2	A	B	Formula
291946	Ph	H	-CH2CH2-	bond	C ₂₄ H ₂₃ NO ₄
291947	CH2Ph	H	(Z)-CH=CH-	O	C ₂₅ H ₂₃ NO ₅
291948	Ph	H	(Z)-CH=CH-	O	C ₂₄ H ₂₁ NO ₅
291949	Ph	H	(Z)-CH2CH=CH-	O	C ₂₅ H ₂₃ NO ₅
291950	Ph	Me	(Z)-CH=CH-	O	C ₂₅ H ₂₃ NO ₅
291951	Ph	H	(E)-CH=CH-	O	C ₂₄ H ₂₁ NO ₅
291952	Ph	H	(Z)-CH=CH-	bond	C ₂₅ H ₂₃ NO ₄

The compounds of the invention are reported to be active in a canine model of intermittent claudication.

SOURCE – Roche.

REFERENCES

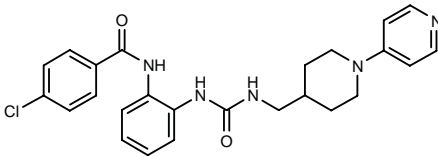
1. Lopez-Tapia, F.J. et al. (F. Hoffmann-La Roche AG) *Aryl carboxylic acid and tetrazole derivs. comprising a carbamoyloxy unit.* EP 1013639.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

290462

4-Chloro-*N*-[2-[3-[1-(4-pyridyl)-4-piperidinylmethyl]ureido]-phenyl]benzamide



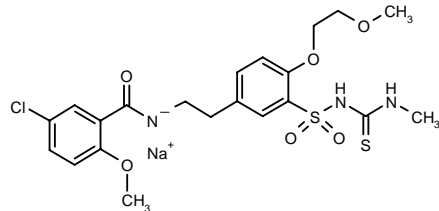
C25 H26 Cl N5 O2; Mol wt: 463.9664

ANTIARRHYTHMIC DRUGS

HMR-1402

241812

5-Chloro-2-methoxy-*N*-[2-[4-(2-methoxyethoxy)-3-(3-methylthioureidosulfonyl)phenyl]ethyl]benzamide



C21 H25 Cl N3 O6 S2 . Na; Mol wt: 538.0185

ACTION – Cardiselective ATP-sensitive potassium (K_{ATP}) channel antagonist proven to be more potent than glibenclamide in inhibiting rilmakalim-induced shortening of the APD_{90} in guinea pig papillary muscle (IC_{50} = 98 and 140 nM, respectively). In dogs with healed myocardial infarction subjected to coronary occlusion during exercise, both compound (3.0 mg/kg i.v., 4 μ g/kg/min for 1 h prior to exercise) and glibenclamide (1.0 mg/kg i.v.) prevented ventricular fibrillation in almost all animals. However, unlike glibenclamide, compound was not associated with effects on coronary blood flow, plasma insulin or blood glucose. Potentially useful as an antiarrhythmic agent.

SOURCE – Aventis Pharma.

REFERENCES

1. Englert, H.C. et al. (Aventis SA) *Substd. benzenesulfonylureas and -thiureas, process for their preparation, their use as medicament or diagnostic agent, as well as medicaments containing them.* DE 19505397, EP 0727416, JP 1996245554, US 5652268.

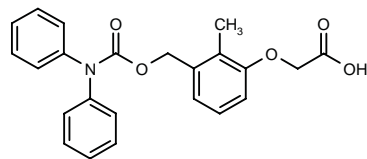
2. Billman, G.E. et al. *HMR 1402, a novel cardiselective ATP-sensitive potassium channel antagonist, prevents ventricular fibrillation induced by myocardial ischemia.* Circulation 2000, 102(18, Suppl.): Abst 1012.

3. Billman, G.E. et al. *HMR 1402, a novel cardiselective ATP-sensitive potassium channel antagonist, protects against ischaemically-induced ventricular fibrillation.* Eur Heart J 2000, 21(Suppl.): Abst P1766.

TREATMENT OF PERIPHERAL VASCULAR DISEASE

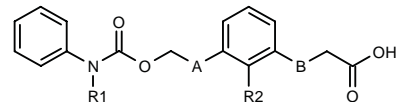
291945

2-[3-(*N,N*-Diphenylcarbamoyloxymethyl)-2-methylphenoxy]acetic acid



C23 H21 N O5; Mol wt: 391.4209

ACTION – Prostaglandin I_2 (IP) receptor agonist, potentially useful for accelerating wound healing and for the treatment of tissue necrosis, premature uterine contractions, gastric ulcer, sexual dysfunction, severe menstrual pain and disorders related to inadequate immunoregulation, platelet aggregation and neutrophil function. Preferably, the compound may be of use for the treatment of cardiovascular disorders including peripheral arterial occlusive disease, intermittent claudication, atherosclerosis, coronary artery disease, stroke, etc. Other specifically claimed compounds are:



Compound	R1	R2	A	B	Formula
291946	Ph	H	-CH2CH2-	bond	C ₂₄ H ₂₃ NO ₄
291947	CH2Ph	H	(Z)-CH=CH-	O	C ₂₅ H ₂₃ NO ₅
291948	Ph	H	(Z)-CH=CH-	O	C ₂₄ H ₂₁ NO ₅
291949	Ph	H	(Z)-CH2CH=CH-	O	C ₂₅ H ₂₃ NO ₅
291950	Ph	Me	(Z)-CH=CH-	O	C ₂₅ H ₂₃ NO ₅
291951	Ph	H	(E)-CH=CH-	O	C ₂₄ H ₂₁ NO ₅
291952	Ph	H	(Z)-CH=CH-	bond	C ₂₅ H ₂₃ NO ₄

The compounds of the invention are reported to be active in a canine model of intermittent claudication.

SOURCE – Roche.

REFERENCES

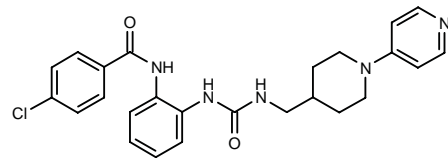
1. Lopez-Tapia, F.J. et al. (F. Hoffmann-La Roche AG) *Aryl carboxylic acid and tetrazole derivs. comprising a carbamoyloxy unit.* EP 1013639.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

290462

4-Chloro-*N*-[2-[3-[1-(4-pyridyl)-4-piperidinylmethyl]ureido]-phenyl]benzamide



C25 H26 Cl N5 O2; Mol wt: 463.9664

ACTION – Anticoagulant, a factor Xa inhibitor with > 500-fold selectivity over bovine trypsin, other coagulation factors (IIa, XIa, XIIa and activated protein C) and fibrinolytic enzymes such as plasmin, t-PA and urokinase. Compound was very active in the prothrombin time assay, the concentration required to double the time to clot formation being about 0.58 μ M. *In vivo* in a rabbit arteriovenous shunt model, compound given by 30-min continuous i.v. infusion showed dose-dependent anti-thrombotic efficacy (ED₅₀ = 1.8 mg/kg/h).

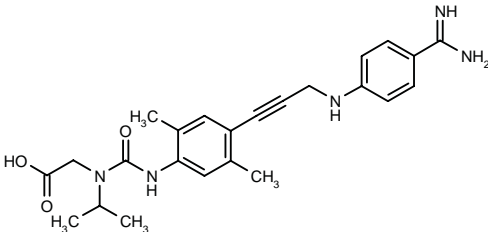
SOURCE – Lilly.

REFERENCES

1. Beight, D.W. et al. (Eli Lilly and Company) *Antithrombotic agents*. WO 9900121.
2. Masters, J.J. et al. *Non-amidine-containing 1,2-dibezamidobenzene inhibitors of human factor Xa with potent anticoagulant and antithrombotic activity*. J Med Chem 2000, 43(11): 2087.

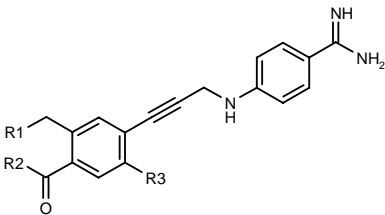
291656

2-[3-[4-[3-(4-Amidinophenylamino)-1-propynyl]-2,5-dimethylphenyl]-1-isopropylureido]acetic acid



C24 H29 N5 O3; Mol wt: 435.5251

ACTION – Antithrombotic agent with the ability to prolong the activated partial thromboplastin time (aPTT) in human plasma (ED₂₀₀ = 0.20 μ M). Other specifically claimed substituted aryl and heteroaryl derivatives include the following:



Compound	R1	R2	R3	Formula
291657	CO2Et	2-Me-1-pyrrolidinyl	Me	C ₂₇ H ₃₂ N ₄ O ₃
291658	H	2-Me-1-pyrrolidinyl	Me	C ₂₄ H ₂₈ N ₄ O
291659	H	i-Pr	Me	C ₂₂ H ₂₆ N ₃ O
291660	H	2-Pyr-N(Me)	Me	C ₂₅ H ₂₆ N ₃ O
291661	H	1-pyrrolidinyl	H	C ₂₂ H ₂₄ N ₄ O

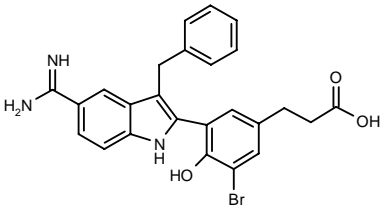
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Priepke, H. et al. (Boehringer Ingelheim Pharma KG) *Substd. aryl and heteroaryl derivs., their production and their use as medicines*. DE 19858029, WO 0035859.

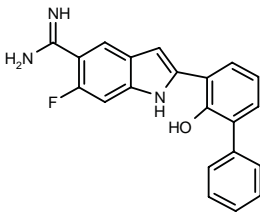
291714

3-[3-(5-Amidino-3-benzyl-1*H*-indol-2-yl)-5-bromo-4-hydroxyphenyl]propionic acid



C25 H22 Br N3 O3; Mol wt: 492.3708

ACTION – Serine protease inhibitor with selectivity for factor Xa, exhibiting K_i values of 0.000618 and 0.26 μ M, respectively, when tested for inhibition of human factor Xa and urokinase-type plasminogen activator. It is expected to be of use as an anticoagulant for the treatment of thromboembolic disorders. Another exemplified compound is:



291715: C21 H16 F N3 O

The invention also includes urokinase inhibitors useful for the treatment of cancer (see 291712).

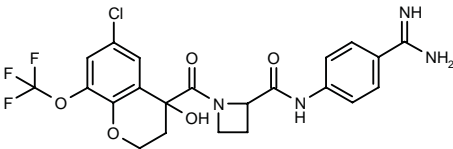
SOURCE – Axys Pharmaceuticals.

REFERENCES

1. Allen, D.A. et al. (Axys Pharmaceuticals, Inc.) *Protease inhibitors*. WO 0035886.

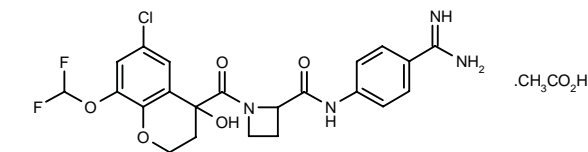
291735

N-(4-Amidinophenyl)-1-[6-chloro-4-hydroxy-8-(trifluoromethoxy)-3,4-dihydro-2*H*-1-benzopyran-4-ylcarbonyl]-azetidine-2-carboxamide



C22 H20 Cl F3 N4 O5; Mol wt: 512.8700

ACTION – Competitive inhibitor of trypsin-like serine proteases, especially thrombin, useful for the treatment of thrombosis and related disorders. The compound was found to increase thrombin clotting time in human plasma with an IC₅₀ < 0.1 μ M. Another exemplified compound from this series of amidino derivatives is:



291736: C22 H21 Cl F2 N4 O5 . C2 H4 O2

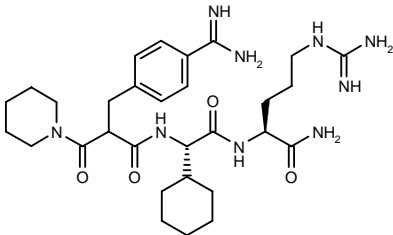
SOURCE – AstraZeneca.

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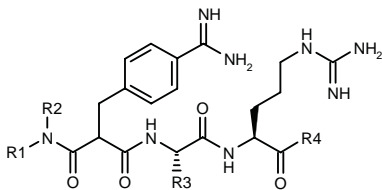
291954

N-[*N*-[3-(4-Amidinophenyl)-2-(1-piperidinylicarbonyl)-propionyl]-2(*S*)-cyclohexylglycyl]-L-argininamide

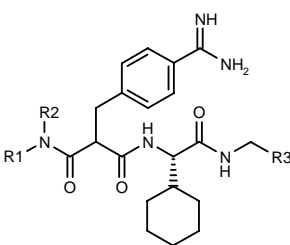


C30 H47 N9 O4; Mol wt: 597.7603

ACTION – Anticoagulant, a factor Xa inhibitor ($K_i = 0.0035 \mu\text{M}$ against human factor Xa), potentially useful for the treatment of thromboembolic diseases. Other specifically claimed malonic acid derivatives are:



Compound	R1	R2	R3	R4	Formula
291955	H	CH2Ph	cyclohexyl	4-Ph-1-Piz	C ₄₂ H ₅₆ N ₁₀ O ₄
291957	-CH2CH2OCH2CH2-		Bu	NH2	C ₂₇ H ₄₃ N ₉ O ₅
291958	-CH2CH2OCH2CH2-		Ph	NH2	C ₂₉ H ₃₉ N ₉ O ₅
291959		-(CH2)5-	Ph	NH2	C ₃₀ H ₄₁ N ₉ O ₄
291960	Me	Me	Ph	4-(7-Cl-2-Naph-SO2)-1-Piz	C ₄₁ H ₅₅ ClN ₁₀ O ₆ S
291961	Me	Me	cyclohexyl	NH2	C ₂₇ H ₄₃ N ₉ O ₄



Compound	R1	R2	R3	Isomer	Formula
291956	Me	Me	4-[NH2C(=NH)]-Ph		C ₂₉ H ₃₉ N ₇ O ₃
291962	H	CH2Ph	4-[NH2C(=NH)]-Ph	R	C ₃₄ H ₄₁ N ₇ O ₃
291963	H	CH2Ph	1-[NH2C(=NH)]-4-Pip		C ₃₃ H ₄₆ N ₆ O ₃
291964	Me	Me	4-[NH2C(=NH)]-1-Pip		C ₂₈ H ₄₄ N ₆ O ₃

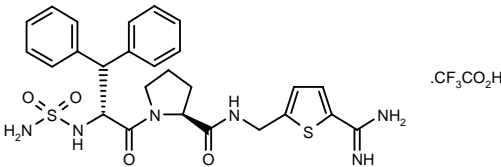
SOURCE – Aventis Pharma.

REFERENCES

1. Defossa, E. et al. (Aventis Pharma Deutschland GmbH) *Novel malonic acid derivs., processes for their preparation, their use and pharmaceutical compsns. containing them (inhibition of factor Xa activity)*. EP 1016663, WO 0040571.

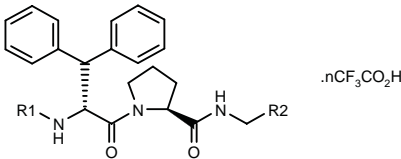
292090

N-Sulfamoyl-D-diphenylalanyl-L-proline 5-amidinothien-2-ylmethyl amide trifluoroacetate



C26 H30 N6 O4 S2 . C2 H F3 O2; Mol wt: 668.7149

ACTION – Antithrombotic agent and anticoagulant with potent inhibitory activity against thrombin ($K_i = 0.003 \text{ nM}$) and high oral bioavailability in rats. Other exemplified compounds are:



Compound	R1	R2	n	Formula
292091	SO2Me	5-[NH2C(=NH)]-2-thienyl	1	C ₂₇ H ₃₁ N ₅ O ₄ S ₂ .C ₂ HF ₃ O ₂
292092	SO2NH2	4-[NH2C(=NH)]-2-thienyl	1	C ₂₆ H ₃₀ N ₆ O ₄ S ₂ .C ₂ HF ₃ O ₂
292093	SO2NH2	5-[NH2C(=NH)]-3-thienyl	1	C ₂₆ H ₃₀ N ₆ O ₄ S ₂ .C ₂ HF ₃ O ₂
292094	CO2Me	5-[NH2C(=NH)]-3-thienyl	1	C ₂₈ H ₃₁ N ₅ O ₄ S ₂ .C ₂ HF ₃ O ₂
292095	CH2CO2H	5-[NH2C(=NH)]-2-thienyl	2	C ₂₈ H ₃₁ N ₅ O ₄ S ₂ .2C ₂ HF ₃ O ₂
292096	CH2CH2-CO2H	5-[NH2C(=NH)]-2-thienyl	2	C ₂₉ H ₃₃ N ₅ O ₄ S ₂ .2C ₂ HF ₃ O ₂

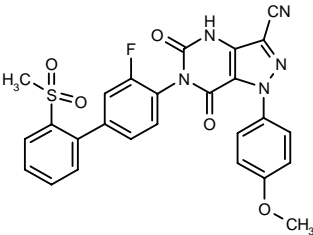
SOURCE – LG Chem.

REFERENCES

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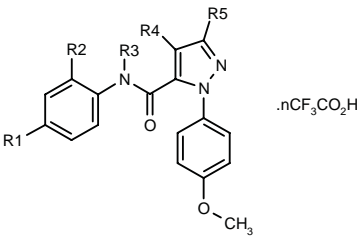
292177

6-[3-Fluoro-2'-(methylsulfonyl)biphenyl-4-yl]-1-(4-methoxyphenyl)-5,7-dioxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonitrile

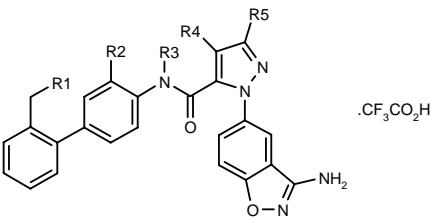


C26 H18 F N5 O5 S; Mol wt: 531.5222

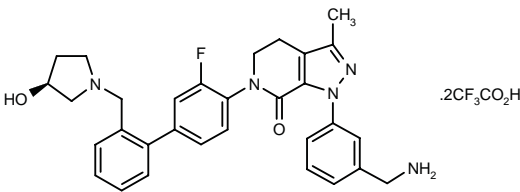
ACTION – Anticoagulant, a factor Xa inhibitor potentially useful for the treatment of thromboembolic disorders. Other exemplified nitrogen-containing heterobicycles include the following:



Compound	R1	R2	R3,R4	R5	n	Formula
292178	2-Me- -1-imidazolyl	H	-CONH-	CONH2	0	C ₂₃ H ₁₉ N ₇ O ₄
292179	2-[N(Me)2- CH2]-Ph	H	-CONH-	CN	1	C ₂₈ H ₂₄ N ₆ O ₃ .C ₂ HF ₃ O ₂
292180	2-(MeSO2)-Ph	F	-CONH-	CH2NHCHO	0	C ₂₇ H ₂₂ FN ₅ O ₆ S
292184	2-(1-pyrrolidinyl- CH2)-Ph	H	-C(Me)=N-	2-tetra- zoly-CH2	1	C ₃₂ H ₃₁ N ₉ O ₂ .C ₂ HF ₃ O ₂
292186	3-[N(Me)2- CH2]-Ph	F	-(CH2)3-	CF3	1	C ₂₈ H ₂₂ F ₃ N ₇ O ₂ .C ₂ HF ₃ O ₂



Compound	R1	R2	R3,R4	R5	Formula
292181	3(R)-OH-1-pyrrolidinyl	F	-(CH2)3-	CF3	C ₃₂ H ₂₈ F ₄ N ₆ O ₃ .C ₂ HF ₃ O ₂
292182	N(Me)2	H	-(CH2)2-	Me	C ₂₉ H ₂₈ N ₆ O ₂ .C ₂ HF ₃ O ₂
292183	3(R)-OH-1-pyrrolidinyl	F	-(CH2)2-	CF3	C ₃₁ H ₂₆ F ₄ N ₆ O ₃ .C ₂ HF ₃ O ₂
292185	N(Me)2	H	-CH=N-	CF3	C ₃₂ H ₃₁ N ₉ O ₂ .C ₂ HF ₃ O ₂



292187: C31 H32 F N5 O2 . 2 C2 H F3 O2

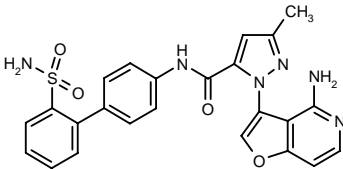
SOURCE – DuPont Pharmaceuticals.

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1. Fevig, J.M. et al. (DuPont Pharmaceuticals Co.) *Nitrogen containing heterobicycles as factor Xa inhibitors*. WO 0039131.

292190

1-(4-Aminofuro[3,2-*c*]pyridin-3-yl)-*N*-(2'-sulfamoylbiphenyl-4-yl)-3-methyl-1*H*-pyrazole-5-carboxamide



C24 H20 N6 O4 S; Mol wt: 488.5260

ACTION – A representative compound from a series of nitrogen-containing aromatic heterocycles that inhibits tyrosin-like serine proteases, especially factor Xa, and is potentially useful for the treatment of thromboembolic disorders.

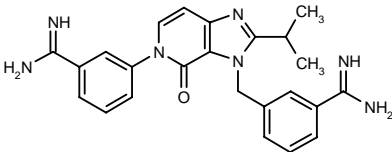
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Lam, P.Y.S. et al. (DuPont Pharmaceuticals Co.) *Thrombin or factor Xa inhibitors*. WO 0038683, WO 0039102, WO 0039108.

292356

3-[5-(3-Amidinophenyl)-2-isopropyl-4-oxo-4,5-dihydro-3*H*-imidazo[4,5-*c*]pyridin-3-ylmethyl]benzamidine



C24 H25 N7 O; Mol wt: 427.5095

ACTION – Factor Xa inhibitor, potentially useful for the treatment of thromboembolic diseases. The compound is specifically claimed for the therapy of thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, restenosis following angioplasty and intermittent claudication.

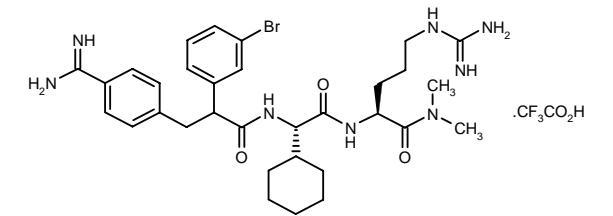
SOURCE – Merck KGaA.

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1. Mederski, W. et al. (Merck Patent GmbH) *Imidazo[4,5-c]pyridine-4-on-derivs*. DE 19900471, WO 0040583.

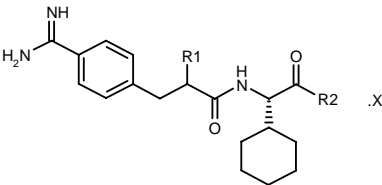
292426

N^α-[3-(4-Amidinophenyl)-2-(3-bromophenyl)propionyl]-L-(2-cyclohexyl)glycyl-L-arginine *N,N*-dimethylamide tri-fluoroacetate



C32 H45 Br N8 O3 . C2 H F3 O2; Mol wt: 783.6864

ACTION – Anticoagulant, a factor Xa inhibitor (*K*_i = 0.7 nM) devoid of significant inhibitory activity against other proteases involved in the blood coagulation pathway. Other exemplified arylalkanoyl derivatives include the following:



Compound	R1	R2	X	Formula
292427	3-Pyr	-L-Arg-NH2	CF3CO2H	C ₂₉ H ₄₁ N ₉ O ₃ .C ₂ HF ₃ O ₂
292428	3-Cl-Ph	-L-Arg-NH2	HCl	C ₃₀ H ₄₁ ClN ₈ O ₃ .HCl
292429	3-Br-Ph	-L-Arg-NH2	HCl	C ₃₀ H ₄₁ BrN ₈ O ₃ .HCl
292430	2-Me-Ph	1-[NH2C(=NH)]-4-Pip-CH2NH	HCl	C ₃₂ H ₄₈ N ₇ O ₂ .HCl
292431	3-Cl-Ph	1-[NH2C(=NH)]-4-Pip-CH2NH	HCl	C ₃₁ H ₄₂ ClN ₇ O ₂ .HCl
292432	4-Br-Ph	1-[NH2C(=NH)]-4-Pip-CH2NH	HCl	C ₃₁ H ₄₂ BrN ₇ O ₂ .HCl
292433	3-Br-Ph	1-[MeC(=NH)]-4-Pip-CH2NH	CF3CO2H	C ₃₂ H ₄₃ BrN ₆ O ₂ .C ₂ HF ₃ O ₂
292434	2-Cl-Ph	1-[NH2C(=NH)]-4-Pip-CH2NH	CF3CO2H	C ₃₁ H ₄₂ ClN ₇ O ₂ .C ₂ HF ₃ O ₂

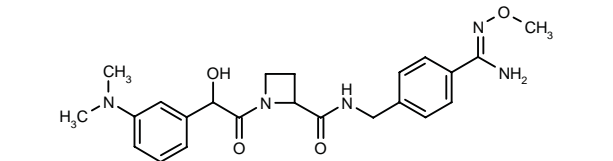
SOURCE – Aventis Pharma.

REFERENCES

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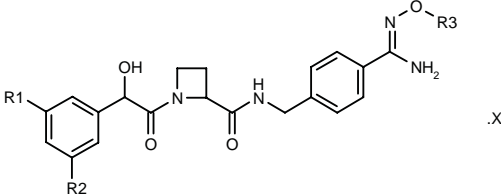
292611

1-[2-[3-(Dimethylamino)phenyl]-2-hydroxyacetyl]-*N*-[4-(*N*-methoxyamidino)benzyl]azetidine-2-carboxamide



C23 H29 N5 O4; Mol wt: 439.5131

ACTION – Anticoagulant and antithrombotic agent with thrombin-inhibitory activity; it acts as a prodrug of the corresponding free amidine, shown to double human thrombin time *in vitro* at a concentration of < 0.5 μM. Other exemplified compounds from this series of amidino-benzylamine derivatives include the following:



Compound	R1	R2	R3	X	Formula
292612	N(Me)2	Cl	Me		C ₂₃ H ₂₈ ClN ₅ O ₄
292613	N(Me)2	Cl	Et		C ₂₄ H ₃₀ ClN ₅ O ₄
292614	N(Me)2	Cl	i-Pr		C ₂₅ H ₃₂ ClN ₅ O ₄
292615	N(Me)Ac	Cl	Me	CF3CO2H	C ₂₄ H ₂₈ ClN ₅ O ₅ .C ₂ HF ₃ O ₂
292616	2-oxo-1-pyrrolidinyl	H	Me	CF3CO2H	C ₂₅ H ₂₉ N ₅ O ₅ .C ₂ HF ₃ O ₂
292617	2-oxo-1-pyrrolidinyl	H	Pr		C ₂₇ H ₃₃ N ₅ O ₅

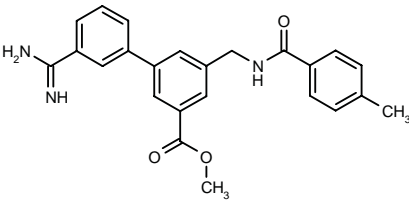
SOURCE – AstraZeneca.

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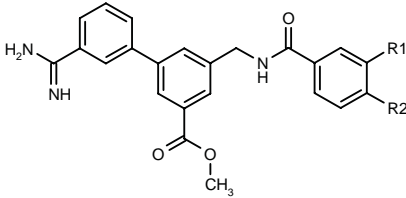
292619

3'-Amidino-5-(4-methylbenzamidomethyl)biphenyl-3-carboxylic acid methyl ester



C24 H23 N3 O3; Mol wt: 401.4637

ACTION – Anticoagulant and antithrombotic agent, a human factor Xa inhibitor (IC₅₀ = 0.1-1 μM). A representative compound from a series of biphenylamidine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
292620	H	OMe	C ₂₄ H ₂₃ N ₃ O ₄
292621	H	NHMe	C ₂₄ H ₂₄ N ₄ O ₃
292622	H	N(Me)2	C ₂₅ H ₂₆ N ₄ O ₃
292623	Me	Me	C ₂₅ H ₂₅ N ₃ O ₃
292625	H	Et	C ₂₅ H ₂₅ N ₃ O ₃
292626	H	i-Pr	C ₂₆ H ₂₇ N ₃ O ₃

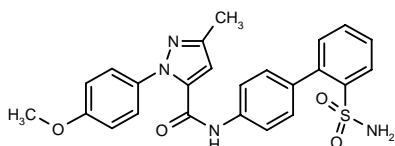
SOURCE – Teijin.

REFERENCES

1. Tsutsumi, T. et al. (Teijin Ltd.) *Biphenylamidine derivs.* JP 2000178243.

292656

1-(4-Methoxyphenyl)-3-methyl-*N*-(2'-sulfamoylbiphenyl-4-yl)-1*H*-pyrazole-5-carboxamide



C24 H22 N4 O4 S; Mol wt: 462.5278

ACTION – Oral anticoagulant, an inhibitor of factor Xa ($K_i = 11$ nM) with high selectivity over thrombin and trypsin ($K_i > 21,000$ and > 1500 nM, respectively). Compound exhibited improved oral bioavailability and a longer half-life ($F = 48\%$, $t_{1/2} = 4.46$ h) in comparison to the parent cationic factor Xa inhibitor SN-429.

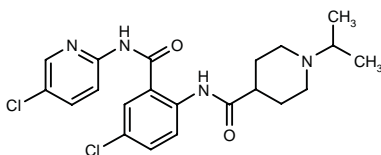
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Galembo, R.A. Jr. et al. (The DuPont Merck Pharmaceutical Company) *Inhibitors of factor Xa with a neutral P1 specificity group.* US 5998424, WO 9857937.
2. Galembo, R.A. Jr. et al. *New functional groups for interaction with the S1 pocket of factor Xa: The discovery of 1-(4-methoxyphenyl)pyrazole inhibitors.* 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 290.

292674

N-[4-Chloro-2-[*N*-(5-chloropyridin-2-yl)carbamoyl]phenyl]-1-isopropylpiperidine-4-carboxamide



C21 H24 Cl2 N4 O2; Mol wt: 435.3526

ACTION – Anticoagulant, a factor Xa inhibitor able to double human prothrombin time at 300 nM and producing plasma levels exceeding the concentration required to prolong human prothrombin time for over 24 h in dogs following a dose of 10 mg/kg p.o. In a canine coronary thrombosis model, compound at doses of 10-15 mg/kg p.o. demonstrated good antithrombotic efficacy, significantly increasing the time to occlusion.

SOURCE – Lilly.

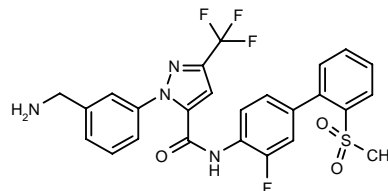
REFERENCES

1. Kyle, J.A. et al. (Eli Lilly and Company) *Aromatic amides.* WO 0039118.
2. Kyle, J.A. et al. *SAR investigations of N-aryl-2-[(piperidin-4-ylcarbonyl)amino]-benzamide factor Xa inhibitors.* 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 288.

DPC-423

290746

1-[3-(Aminomethyl)phenyl]-*N*-[3-fluoro-2'-(methylsulfonyl)-biphenyl-4-yl]-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide



C25 H20 F4 N4 O3 S; Mol wt: 532.5160

ACTION – Anticoagulant, a potent, selective and orally bioavailable factor Xa inhibitor ($K_i = 0.15$ nM) selected for clinical evaluation for the treatment of thrombotic disorders.

SOURCE – DuPont Pharmaceuticals.

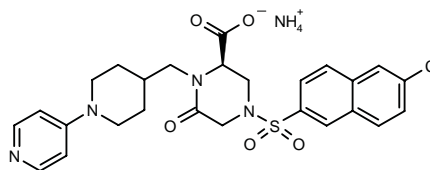
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1. Pinto, D.J.P. et al. (DuPont Pharmaceuticals Co.) *Nitrogen containing heteroaromatics as factor Xa inhibitors.* EP 0946508, WO 9828269.
2. Pinto, D.J.P. et al. (DuPont Pharmaceuticals Co.) *Nitrogen containing heteroaromatics as factor Xa inhibitors.* US 6020357.
3. Jona, J.A. *Salt selection and physicochemical properties of DPC 423.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2572.
4. Lam, P.Y.S. et al. *Structure-based design and discovery of orally-bioavailable potent nonbenzimidazole factor Xa inhibitors.* 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 329.
5. Pinto, D.J. et al. *The discovery of DPC 423, a highly potent, selective and orally bioavailable inhibitor of blood coagulation factor Xa.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-127.
6. Wexler, R.R. et al. *The design and synthesis of orally bioavailable noncovalent factor Xa inhibitors.* 27th Natl Med Chem Symp (June 13-17, Kansas City) 2000, Abst S-14.
7. Wong, P.C. et al. *Antithrombotic effects of DPC 423, a potent and orally active nonpeptide factor Xa inhibitor, in rabbit models of thrombosis.* Circulation 2000, 102(18, Suppl.): Abst 625.

M-55555

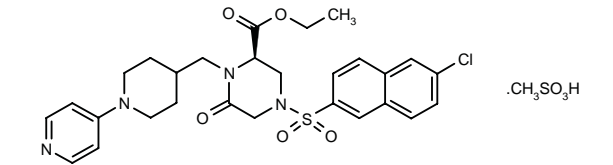
293370

4-(6-Chloronaphthalen-2-ylsulfonyl)-6-oxo-1-[1-(4-pyridinyl)piperidin-1-ylmethyl]piperazine-2(*R*)-carboxylic acid ammonium salt



C26 H26 Cl N4 O5 S . H4 N; Mol wt: 560.0720

ACTION – Anticoagulant, an inhibitor of factor Xa with a K_i value of approximately 3 nM, inactive (up to 10 μ M) against human trypsin, thrombin, activated protein C, plasmin, t-PA and urokinase. In the thromboplastin-induced thrombosis model in rats, compound given at a dose of 0.3 mg/kg i.v. inhibited thrombus formation without significantly prolonging bleeding time even at 3 mg/kg i.v. **M-55190**, the orally active ester form, showed similar activity at 3 mg/kg p.o. and did not prolong bleeding time significantly at up to 100 mg/kg p.o.



M-55190* [279443]: C28 H31 Cl N4 O5 S . C H4 O3 S

SOURCE – Mochida.

REFERENCES

1. Nishida, H. et al. (Mochida Pharmaceutical Co., Ltd.) *Aromatic cpds. having cyclic amino or salts thereof*. EP 1048652, WO 9933805.

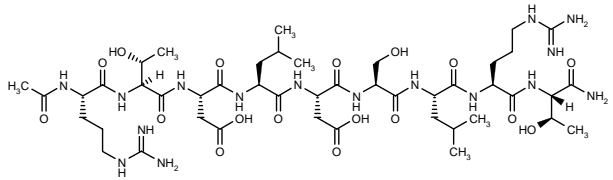
2. Nishida, H. et al. *Synthesis and biological activities of the 2-piperazinone derivative (M55190), an orally active and highly specific factor Xa inhibitor*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-125.

*Identified compound **279443** (see **279436**) Drug Data Rep 1999, 021(10): 0888.

ANTIPLATELET THERAPY

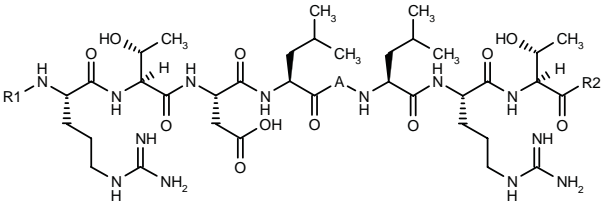
291764

Acetyl-L-arginyl-L-threonyl-L-aspartyl-L-leucyl-L-aspartyl-L-seryl-L-leucyl-L-arginyl-L-threoninamide



C45 H80 N16 O17; Mol wt: 1117.2220

ACTION – Inhibitor of the $\alpha_v\beta_6$ integrin receptor, particularly useful for the treatment of angiogenesis, thrombosis, myocardial infarction, coronary artery disease, arteriosclerosis, tumors, osteoporosis, inflammation, infection and wound-healing disorders. The compound exhibited an IC_{50} ratio relative to a standard peptide of 0.013 when tested for inhibition of fibrinogen binding to the human $\alpha_v\beta_6$ receptor. Other exemplified peptides are:



Compound	R1	R2	A	Formula
291765	H	-L-Tyr-OH	-L-Tyr-L-Tyr-	C ₆₃ H ₉₄ N ₁₆ O ₁₈
291766	H	NH2	-L-Asp-L-Ser-	C ₄₃ H ₇₈ N ₁₆ O ₁₆
291767	Ac	OH	-L-Asp-L-Ser-	C ₄₅ H ₇₉ N ₁₅ O ₁₈

SOURCE – Merck KGaA.

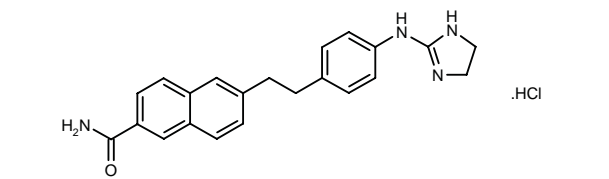
REFERENCES

1. Diefenbach, B. et al. (Merck Patent GmbH) *$\alpha_v\beta_6$ Integrin inhibitors*. WO 0037487.

THROMBOLYTICS

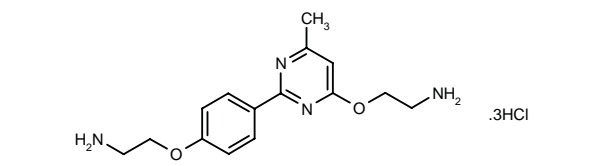
291722

6-[2-[4-(4,5-Dihydro-1H-imidazol-2-ylamino)phenyl]ethyl]naphthalene-2-carboxamide hydrochloride

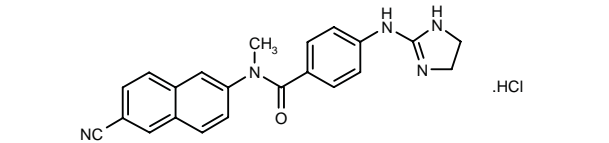


C22 H22 N4 O . HCl; Mol wt: 394.9037

ACTION – Antithrombotic agent with fibrinolysis-accelerating effects. It was found to promote plasmin formation *in vitro* and protected mice against thrombin-induced pulmonary thrombosis, affording a survival rate of 73.3% at a dose of 0.1 mg/kg i.v. Other benzene derivatives from this series are:



291723: C15 H20 N4 O2 . 3HCl



291724: C22 H19 N5 O . HCl

SOURCE – Torii.

REFERENCES

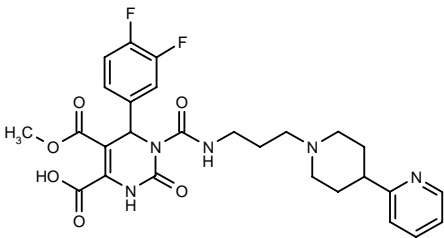
1. Nakatogawa, K. et al. (Torii Pharmaceutical Co., Ltd.) *Benzene derivs*. JP 2000159751.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

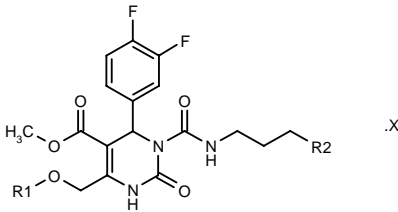
291807

6-(3,4-Difluorophenyl)-5-(methoxycarbonyl)-2-oxo-1-[N-[3-[4-(2-pyridyl)piperidin-1-yl]propyl]carbamoyl]-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid

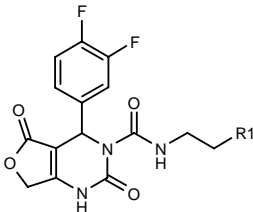


C27 H29 F2 N5 O6; Mol wt: 557.5511

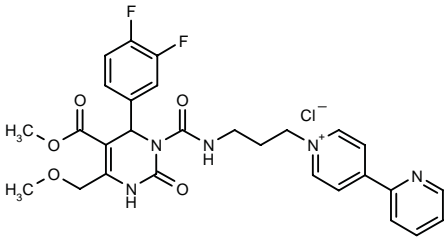
ACTION – Selective human α_{1A} -adrenoceptor antagonist, as demonstrated in binding assays using cloned human α_{1A} -, α_{1B} -, α_{1D} -, α_{2A} -, α_{2B} - and α_{2C} -adrenoceptors. Potentially useful for the treatment of benign prostatic hyperplasia. Other exemplified dihydropyrimidines include the following:



Compound	R1	R2	Formula
291808	Me	OH	C ₁₈ H ₂₁ F ₂ N ₅ O ₆
291809	Me	4-(1-oxido-2-Pyr)-1-Pip	C ₂₈ H ₃₃ F ₂ N ₅ O ₆
291811	Me	1-oxido-4-(2-Pyr)-1-Pip	C ₂₈ H ₃₃ F ₂ N ₅ O ₆
291812	Me	4-OH-4-(2-Pyr)-1-Pip	C ₂₈ H ₃₃ F ₂ N ₅ O ₆
291813	H	4-(2-Pyr)-1-Pip	C ₂₇ H ₃₁ F ₂ N ₅ O ₅



Compound	R1	Formula
291814	4-(2-Pyr)-1-Pip-CH2	C ₂₆ H ₂₇ F ₂ N ₅ O ₄
291815	CO2H	C ₁₆ H ₁₃ F ₂ N ₅ O ₆



291810: C28 H28 Cl F2 N5 O5

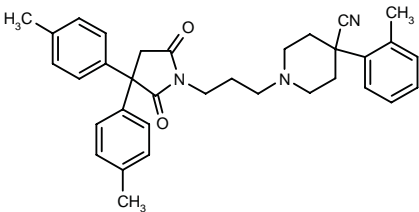
SOURCES – Merck & Co.; Synaptic.

REFERENCES

1. Cui, D. et al. (Synaptic Pharmaceutical Corp.;Merck & Co., Inc.) *Dihydropyrimidines and uses thereof*. WO 0037026.

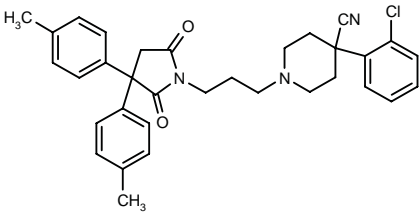
292675

1-[3-[3,3-Bis(4-methylphenyl)-2,5-dioxopyrrolidin-1-yl]propyl]-4-(2-methylphenyl)piperidine-4-carbonitrile



C34 H37 N3 O2; Mol wt: 519.6853

ACTION – Potent and selective α_{1A} -adrenoceptor antagonist with nanomolar affinity for this subtype (K_i = 1.7 nM) and > 800-fold selectivity over α_{1B} - and α_{1D} -adrenoceptors (K_i = 1900 and 1500 nM, respectively), and potential in the treatment of benign prostatic hyperplasia (BPH). Compound exhibited only modest improvement in pharmacokinetics (oral bioavailability of 18 and 8%, respectively, in rats and dogs) compared with the prototype phenylacetamides. Another cyclic imide compound with a similar profile is:



292676: C33 H34 Cl N3 O2

SOURCE – Merck & Co.

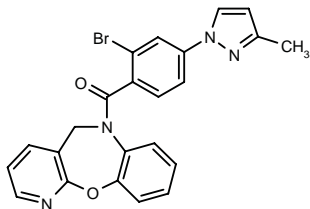
REFERENCES

1. DiPardo, R.M. et al. *Cyclic imides as potent and selective α_{1A} adrenergic receptor antagonists*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 298.

TREATMENT OF URINARY INCONTINENCE

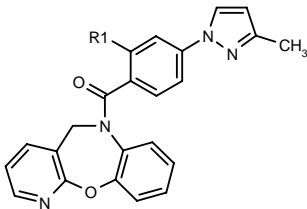
291978

1-[2-Bromo-4-(3-methyl-1*H*-pyrazol-1-yl)phenyl]-1-[5,6-dihydropyrido[2,3-*b*][1,5]benzoxazepin-6-yl]methanone



C23 H17 Br N4 O2; Mol wt: 461.3173

ACTION – Tricyclic vasopressin V₂ receptor agonist, potentially useful in the treatment of diabetes insipidus, nocturnal enuresis, nocturia, urinary incontinence, bleeding and coagulation disorders and for the temporary delay of urination. The compound is reported to have no V_{1a} receptor-agonist effects and therefore does not raise blood pressure. Other specifically claimed compounds are:



Compound	R1	Formula
291979	CF3	C ₂₄ H ₁₇ F ₃ N ₄ O ₂
291980	F	C ₂₃ H ₁₇ FN ₄ O ₂
291981	Cl	C ₂₃ H ₁₇ ClN ₄ O ₂

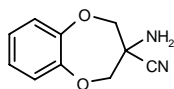
SOURCE – American Home Products.

REFERENCES

1. Failli, A.A. et al. (American Home Products Corp.) *Tricyclic vasopressin agonists*. US 6090803.

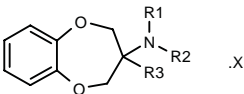
292061

3-Amino-3,4-dihydro-2*H*-1,5-benzodioxepin-3-carbonitrile



C10 H10 N2 O2; Mol wt: 190.2010

ACTION – Compound with affinity for the muscarinic M₃ receptor, potentially useful for the treatment of urinary disorders such as urinary incontinence and pollakiuria, for the modulation of gastrointestinal motility and for the treatment of asthma, and as an antispasmodic and mydriatic agent. Other exemplified 3,4-dihydro-2*H*-1,5-benzodioxepines are:



Compound	R1	R2	R3	X	Formula
292062	Me	Me	CH ₂ NH ₂		C ₁₂ H ₁₈ N ₂ O ₂
292063	H	H	CO ₂ H	HCl	C ₁₀ H ₁₁ NO ₄ ·HCl
292064	COCH ₂ Ph	H	CO ₂ Me		C ₁₉ H ₁₉ NO ₅

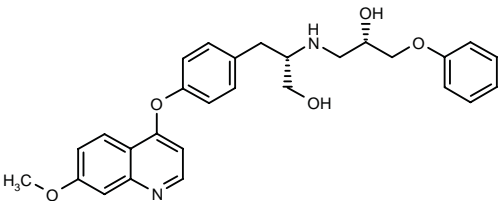
SOURCE – Welfide.

REFERENCES

1. Sonda, S. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *3,4-Dihydro-2H-1,5-benzodioxepine cpds*. JP 2000169468.

292357

2(*S*)-[2(*S*)-Hydroxy-3-phenoxypropylamino]-3-[4-(7-methoxyquinolin-4-yloxy)phenyl]propan-1-ol



C28 H30 N2 O5; Mol wt: 474.5540

ACTION – β₃-Adrenoceptor agonist with potential utility in the treatment of urinary incontinence, pollakiuria, ulcers and pancreatitis, and as a lipolytic. The compound produced significant inhibition of carbachol-induced increases in intravesical pressure in anesthetized dogs at 0.32 mg/kg i.d. administered 30 min before carbachol, with an increase of 5.5 mmHg versus 9.3 mmHg in controls.

SOURCE – Fujisawa.

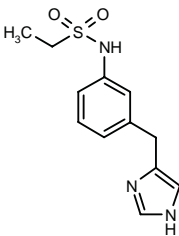
REFERENCES

1. Taniguchi, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Aminoalcohol derivs. and their use as β₃-adrenergic agonists*. WO 0040560.

ABT-866^{1,2,4}

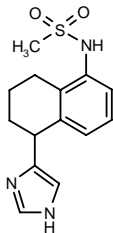
292517

N-[3-(1*H*-Imidazol-4-ylmethyl)phenyl]ethanesulfonamide



C12 H15 N3 O2 S; Mol wt: 265.3355

ACTION – α_{1A} -Adrenoceptor agonist, as demonstrated in a functional assay (EC_{50} = 0.61 μ M; 80% efficacy), a derivative of the potent α_{1A} -agonist **A-204176** with superior uroselectivity *in vivo* in dogs. Potentially useful for the treatment benign prostatic hyperplasia.



A-204176 [286332]*,1,3,4: C14 H17 N3 O2 S

SOURCE – Abbott.

REFERENCES

1. Altenbach, R.J. et al. (Abbott Laboratories Inc.) *Imidazoles and related cpds. as α_{1A} agonists*. WO 0007997.

2. Altenbach, R.J. et al. *ABT-866, a novel α_1 -adrenoceptor ligand with an enhanced in vitro and in vivo profile relative to phenylpropanolamine (PPA) and midodrine*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 294.

3. Brioni, J.D. et al. *Pharmacological effects of a selective α_{1A} adrenoceptor agonist, A-204176, on urethral function*. J Urol 2000, 163(4, Suppl.): Abst 180.

4. Khilevich, A. et al. *Synthesis and structure activity studies on a series of imidazoles as α_{1A} adrenoceptor agonists*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 293.

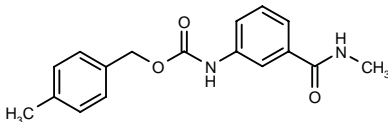
*Identified compound **286332** Drug Data Rep 2000, 022(05): 0437.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

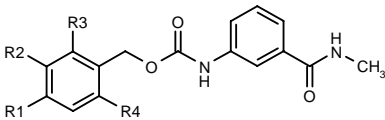
291781

N-[3-(Methylcarbamoyl)phenyl]carbamic acid 4-methylbenzyl ester



C17 H18 N2 O3; Mol wt: 298.3402

ACTION – Anti-*Helicobacter pylori* agent giving an MIC value of 0.10 μ g/ml against *H. pylori* strain 31A. Other exemplified amide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
291782	H	-CH=CHCH=CH-	H	H	C ₂₀ H ₁₈ N ₂ O ₃
291783	-CH=CHCH=CH-	H	H	H	C ₂₀ H ₁₈ N ₂ O ₃
291784	Cl	H	H	H	C ₁₆ H ₁₅ ClN ₂ O ₃
291785	H	Cl	Cl	H	C ₁₆ H ₁₄ Cl ₂ N ₂ O ₃
291786	H	H	Cl	Cl	C ₁₆ H ₁₄ Cl ₂ N ₂ O ₃

SOURCE – Mitsubishi-Tokyo Pharmaceuticals.

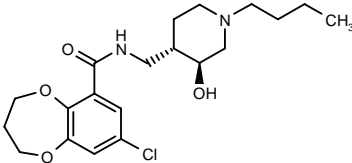
REFERENCES

1. Ando, R. and Chiba, N. (Mitsubishi Chemical Corp.) *Amide derivs*. WO 0037434.

AGENTS FOR IRRITABLE BOWEL SYNDROME THERAPY

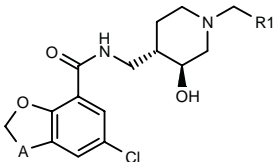
292005

trans-*N*-(1-Butyl-3-hydroxypiperidin-4-ylmethyl)-8-chloro-3,4-dihydro-2*H*-1,5-benzodioxepin-6-carboxamide



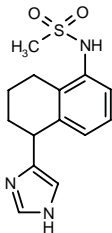
C20 H29 Cl N2 O4; Mol wt: 396.9121

ACTION – 5-HT₄ receptor antagonist (pA_2 = 10.65 in rat esophageal tunica muscularis mucosae), potentially useful in the treatment or prophylaxis of gastrointestinal conditions such as hypermotility, irritable bowel syndrome (IBS), constipation- or diarrhea-predominant IBS, pain- and non-pain-predominant IBS, bowel hypersensitivity and for the reduction of pain associated with gastrointestinal hypersensitivity and/or hyperactivity. It also has potential utility in the treatment of gastric symptoms of gastroesophageal reflux disease (GERD) such as heartburn and in the prophylaxis of dyspepsia. Other exemplified 4-(aminomethyl)-piperidine benzamides include the following:



Compound	R1	A	Formula
292006	Pr	-CH2-	C ₁₉ H ₂₇ ClN ₂ O ₃
292007	Ph	-CH2-	C ₂₂ H ₂₅ ClN ₂ O ₃
292008	2-THF	-(CH2)2-	C ₂₁ H ₂₉ ClN ₂ O ₄
292009	Pr	-CH2O-	C ₁₉ H ₂₇ ClN ₂ O ₄
292010	3-Me-2-pyrazinyl-NHCH2	-CH2O-	C ₂₂ H ₂₆ ClN ₅ O ₄
292011	3-Me-2-pyrazinyl-NHCH2CH2	-CH2O-	C ₂₃ H ₃₀ ClN ₅ O ₄

ACTION – α_{1A} -Adrenoceptor agonist, as demonstrated in a functional assay (EC_{50} = 0.61 μ M; 80% efficacy), a derivative of the potent α_{1A} -agonist **A-204176** with superior uroselectivity *in vivo* in dogs. Potentially useful for the treatment benign prostatic hyperplasia.



A-204176 [286332]*,1,3,4: C14 H17 N3 O2 S

SOURCE – Abbott.

REFERENCES

1. Altenbach, R.J. et al. (Abbott Laboratories Inc.) *Imidazoles and related cpds. as α_{1A} agonists*. WO 0007997.

2. Altenbach, R.J. et al. *ABT-866, a novel α_1 -adrenoceptor ligand with an enhanced in vitro and in vivo profile relative to phenylpropanolamine (PPA) and midodrine*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 294.

3. Brioni, J.D. et al. *Pharmacological effects of a selective α_{1A} adrenoceptor agonist, A-204176, on urethral function*. J Urol 2000, 163(4, Suppl.): Abst 180.

4. Khilevich, A. et al. *Synthesis and structure activity studies on a series of imidazoles as α_{1A} adrenoceptor agonists*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 293.

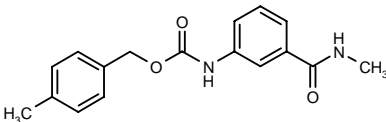
*Identified compound **286332** Drug Data Rep 2000, 022(05): 0437.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

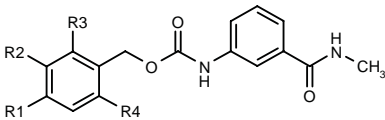
291781

N-[3-(Methylcarbamoyl)phenyl]carbamic acid 4-methylbenzyl ester



C17 H18 N2 O3; Mol wt: 298.3402

ACTION – Anti-*Helicobacter pylori* agent giving an MIC value of 0.10 μ g/ml against *H. pylori* strain 31A. Other exemplified amide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
291782	H	-CH=CHCH=CH-	H	H	C ₂₀ H ₁₈ N ₂ O ₃
291783	-CH=CHCH=CH-	H	H	H	C ₂₀ H ₁₈ N ₂ O ₃
291784	Cl	H	H	H	C ₁₆ H ₁₅ ClN ₂ O ₃
291785	H	Cl	Cl	H	C ₁₆ H ₁₄ Cl ₂ N ₂ O ₃
291786	H	H	Cl	Cl	C ₁₆ H ₁₄ Cl ₂ N ₂ O ₃

SOURCE – Mitsubishi-Tokyo Pharmaceuticals.

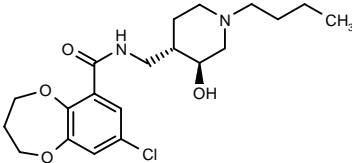
REFERENCES

1. Ando, R. and Chiba, N. (Mitsubishi Chemical Corp.) *Amide derivs*. WO 0037434.

AGENTS FOR IRRITABLE BOWEL SYNDROME THERAPY

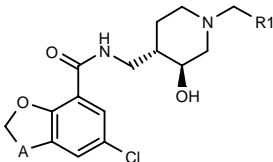
292005

trans-*N*-(1-Butyl-3-hydroxypiperidin-4-ylmethyl)-8-chloro-3,4-dihydro-2*H*-1,5-benzodioxepin-6-carboxamide



C20 H29 Cl N2 O4; Mol wt: 396.9121

ACTION – 5-HT₄ receptor antagonist (pA_2 = 10.65 in rat esophageal tunica muscularis mucosae), potentially useful in the treatment or prophylaxis of gastrointestinal conditions such as hypermotility, irritable bowel syndrome (IBS), constipation- or diarrhea-predominant IBS, pain- and non-pain-predominant IBS, bowel hypersensitivity and for the reduction of pain associated with gastrointestinal hypersensitivity and/or hyperactivity. It also has potential utility in the treatment of gastric symptoms of gastroesophageal reflux disease (GERD) such as heartburn and in the prophylaxis of dyspepsia. Other exemplified 4-(aminomethyl)-piperidine benzamides include the following:



Compound	R1	A	Formula
292006	Pr	-CH2-	C ₁₉ H ₂₇ ClN ₂ O ₃
292007	Ph	-CH2-	C ₂₂ H ₂₅ ClN ₂ O ₃
292008	2-THF	-(CH2)2-	C ₂₁ H ₂₉ ClN ₂ O ₄
292009	Pr	-CH2O-	C ₁₉ H ₂₇ ClN ₂ O ₄
292010	3-Me-2-pyrazinyl-NHCH2	-CH2O-	C ₂₂ H ₂₆ ClN ₅ O ₄
292011	3-Me-2-pyrazinyl-NHCH2CH2	-CH2O-	C ₂₃ H ₃₀ ClN ₅ O ₄

Compound	R1	A	Formula
292012	1,3-dioxolan-2-yl-CH2	-CH2O-	C ₂₀ H ₂₇ ClN ₂ O ₆
292013	2-Me-1,3-dioxolan-2-yl-CH2CH2	-CH2CH2O-	C ₂₃ H ₃₃ ClN ₂ O ₆
292014	1,3-dioxolan-2-yl-CH2	-CH2CH2O-	C ₂₁ H ₃₁ ClN ₂ O ₇
292016	CH2CH2OH	-CH2CH2O-	C ₁₉ H ₂₇ ClN ₂ O ₅
292017	2-THF	-(CH2)3O-	C ₂₂ H ₃₁ ClN ₂ O ₅
292018	CH2CH2CN	-(CH2)3O-	C ₂₁ H ₂₈ ClN ₃ O ₄
292019	CH2CH2OH	-(CH2)3O-	C ₂₀ H ₂₉ ClN ₂ O ₅

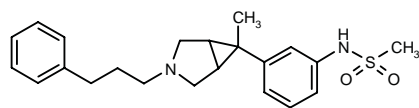
SOURCE – Janssen.

REFERENCES

1. Bosmans, J.-P.R.M.A. et al. (Janssen Pharmaceutica NV) 4-(Aminomethyl)-piperidine benzamides for treating gastrointestinal disorders. WO 0037461.

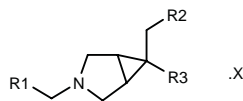
292284

N-[3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl]methanesulfonamide



C22 H28 N2 O2 S; Mol wt: 384.5412

ACTION – Opioid receptor ligand with potential utility in the treatment of diseases modulated by opioid receptors such as irritable bowel syndrome, constipation, nausea, vomiting, pruritus, eating disorders, opiate overdose, depression, smoking and alcohol addiction, sexual dysfunction, etc. Other specifically claimed 3-aza-bicyclo[3.1.0]hexane derivatives are:



Compound	R1	R2	R3	X	Formula
292285	CH2CH2Ph	Me	3-(MeSO2NH)-Ph	CH3CO2H	C ₂₃ H ₃₀ N ₂ O ₂ S .C ₂ H ₄ O ₂
292286	C5H11	H	2-imidazolyl	CH3CO2H	C ₁₅ H ₂₅ N ₃ .C ₂ H ₄ O ₂
292287	CH2CH2Ph	H	3-OH-Ph		C ₂₁ H ₂₅ NO
292288	3-indolyl- -CH2CH2	H	3-(MeSO2NH)-Ph		C ₂₄ H ₂₉ N ₃ O ₂ S
292289	4-F-PhCH2CH2	H	3-(MeSO2NH)-Ph		C ₂₂ H ₂₇ FN ₂ O ₂ S
292290	2-Pyr-CH2CH2	H	3-(MeSO2NH)-Ph		C ₂₁ H ₂₇ N ₃ O ₂ S
292291	6-Me-2-Pyr- -CH=CH	H	3-(MeSO2NH)-Ph		C ₂₂ H ₂₇ N ₃ O ₂ S
292292	2-MeO-Ph- CH2CH2	H	3-(MeSO2NH)-Ph		C ₂₃ H ₃₀ N ₂ O ₃ S

SOURCE – Pfizer.

REFERENCES

1. Banks, B.J. et al. (Pfizer Ltd.;Pfizer Inc.) 3-Azabicyclo[3.1.0]hexane derivs. as opiate receptor ligands. WO 0039089.

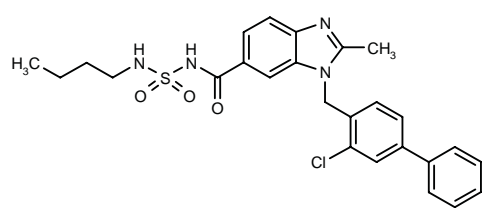
ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

291720

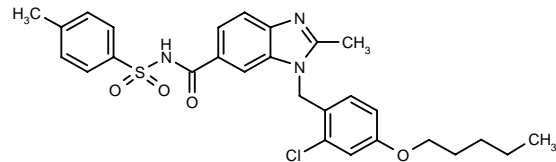
N-Butyl-N'-[1-(3-chlorobiphenyl-4-ylmethyl)-2-methyl-1H-benzimidazol-6-ylcarbonyl]sulfamide

N-(N-Butylsulfamoyl)1-(3-chlorobiphenyl-4-ylmethyl)-2-methyl-1H-benzimidazole-6-carboxamide



C26 H27 Cl N4 O3 S; Mol wt: 511.0433

ACTION – Hypoglycemic and hypotriglyceridemic agent with phosphodiesterase type 5 (PDE5)-inhibitory activity proven to reduce blood sugar and triglyceride levels by 71 and 98%, respectively, in *db/db* mice when given in the diet at 1 mg/kg. Another compound from this series of benzimidazole derivatives is:



291721: C28 H30 Cl N3 O4 S

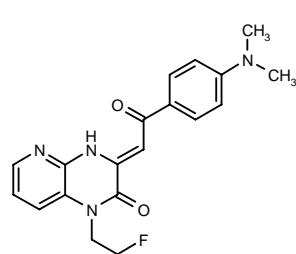
SOURCE – Fujisawa.

REFERENCES

1. Yamasaki, N. et al. (Fujisawa Pharmaceutical Co., Ltd.) Benzimidazole derivs. WO 0039099.

291725

3-[(Z)-2-[4-(Dimethylamino)phenyl]-2-oxoethylidene]-1-(2-fluoroethyl)-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-2-one



C19 H19 F N4 O2; Mol wt: 354.3831

Compound	R1	A	Formula
292012	1,3-dioxolan-2-yl-CH2	-CH2O-	C ₂₀ H ₂₇ ClN ₂ O ₆
292013	2-Me-1,3-dioxolan-2-yl-CH2CH2	-CH2CH2O-	C ₂₃ H ₃₃ ClN ₂ O ₆
292014	1,3-dioxolan-2-yl-CH2	-CH2CH2O-	C ₂₁ H ₃₁ ClN ₂ O ₇
292016	CH2CH2OH	-CH2CH2O-	C ₁₉ H ₂₇ ClN ₂ O ₅
292017	2-THF	-(CH2)3O-	C ₂₂ H ₃₁ ClN ₂ O ₅
292018	CH2CH2CN	-(CH2)3O-	C ₂₁ H ₂₈ ClN ₃ O ₄
292019	CH2CH2OH	-(CH2)3O-	C ₂₀ H ₂₉ ClN ₂ O ₅

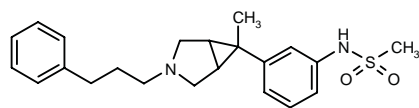
SOURCE – Janssen.

REFERENCES

1. Bosmans, J.-P.R.M.A. et al. (Janssen Pharmaceutica NV) 4-(Aminomethyl)-piperidine benzamides for treating gastrointestinal disorders. WO 0037461.

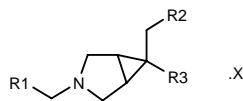
292284

N-[3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl]methanesulfonamide



C22 H28 N2 O2 S; Mol wt: 384.5412

ACTION – Opioid receptor ligand with potential utility in the treatment of diseases modulated by opioid receptors such as irritable bowel syndrome, constipation, nausea, vomiting, pruritus, eating disorders, opiate overdose, depression, smoking and alcohol addiction, sexual dysfunction, etc. Other specifically claimed 3-aza-bicyclo[3.1.0]hexane derivatives are:



Compound	R1	R2	R3	X	Formula
292285	CH2CH2Ph	Me	3-(MeSO2NH)-Ph	CH3CO2H	C ₂₃ H ₃₀ N ₂ O ₂ S .C ₂ H ₄ O ₂
292286	C5H11	H	2-imidazolyl	CH3CO2H	C ₁₅ H ₂₅ N ₃ .C ₂ H ₄ O ₂
292287	CH2CH2Ph	H	3-OH-Ph		C ₂₁ H ₂₅ NO
292288	3-indolyl- -CH2CH2	H	3-(MeSO2NH)-Ph		C ₂₄ H ₂₉ N ₃ O ₂ S
292289	4-F-PhCH2CH2	H	3-(MeSO2NH)-Ph		C ₂₂ H ₂₇ FN ₂ O ₂ S
292290	2-Pyr-CH2CH2	H	3-(MeSO2NH)-Ph		C ₂₁ H ₂₇ N ₃ O ₂ S
292291	6-Me-2-Pyr- -CH=CH	H	3-(MeSO2NH)-Ph		C ₂₂ H ₂₇ N ₃ O ₂ S
292292	2-MeO-Ph- CH2CH2	H	3-(MeSO2NH)-Ph		C ₂₃ H ₃₀ N ₂ O ₃ S

SOURCE – Pfizer.

REFERENCES

1. Banks, B.J. et al. (Pfizer Ltd.;Pfizer Inc.) 3-Azabicyclo[3.1.0]hexane derivs. as opiate receptor ligands. WO 0039089.

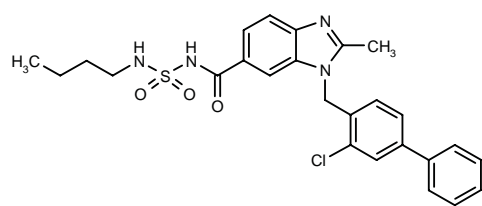
ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

291720

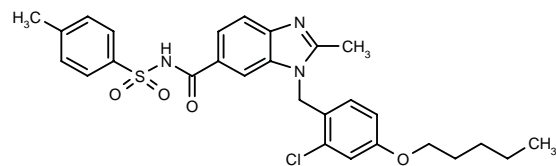
N-Butyl-N'-[1-(3-chlorobiphenyl-4-ylmethyl)-2-methyl-1H-benzimidazol-6-ylcarbonyl]sulfamide

N-(N-Butylsulfamoyl)1-(3-chlorobiphenyl-4-ylmethyl)-2-methyl-1H-benzimidazole-6-carboxamide



C26 H27 Cl N4 O3 S; Mol wt: 511.0433

ACTION – Hypoglycemic and hypotriglyceridemic agent with phosphodiesterase type 5 (PDE5)-inhibitory activity proven to reduce blood sugar and triglyceride levels by 71 and 98%, respectively, in *db/db* mice when given in the diet at 1 mg/kg. Another compound from this series of benzimidazole derivatives is:



291721: C28 H30 Cl N3 O4 S

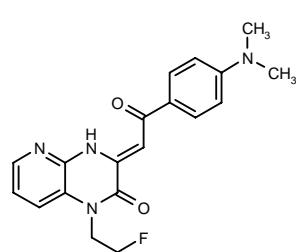
SOURCE – Fujisawa.

REFERENCES

1. Yamasaki, N. et al. (Fujisawa Pharmaceutical Co., Ltd.) Benzimidazole derivs. WO 0039099.

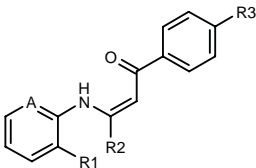
291725

3-[(Z)-2-[4-(Dimethylamino)phenyl]-2-oxoethylidene]-1-(2-fluoroethyl)-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-2-one



C19 H19 F N4 O2; Mol wt: 354.3831

ACTION – Antidiabetic agent that increases insulin secretion, as demonstrated in pancreatic β-cells. A representative compound from a series of condensed cyclic pyrazine derivatives, wherein the following are also included:



Compound	R1,R2	R3	A	Formula
291726	-N(CH2Ph)CO-	N(Me)2	N	C ₂₄ H ₂₂ N ₄ O ₂
291727	-N=C(1-Pip-NH)-	OMe	CH	C ₂₂ H ₂₄ N ₄ O ₂

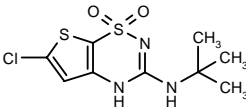
SOURCE – Kyowa Hakko.

REFERENCES

1. Kamisaka, N. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Condensed cyclic pyrazine derivs.* JP 2000154139.

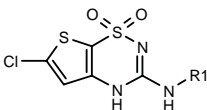
291831

3-(*tert*-Butylamino)-6-chloro-4*H*-thieno[3,2-*e*][1,2,4]-thiadiazine-1,1-dioxide



C9 H12 Cl N3 O2 S2; Mol wt: 293.7978

ACTION – ATP-sensitive potassium (K_{ATP}) channel opener expected to be of use for the treatment of hyperinsulinemia and diabetes. Other specifically claimed 1,2,3-thiadiazine derivatives are:



Compound	R1	Formula
291832	C(Me)2Et	C ₁₀ H ₁₄ ClN ₃ O ₂ S ₂
291833	1-Me-cyclopropyl	C ₉ H ₁₀ ClN ₃ O ₂ S ₂
291834	C(Me)2CH2OH	C ₉ H ₁₂ ClN ₃ O ₃ S ₂
291835	t-BuCH2C(Me)2	C ₁₃ H ₂₀ ClN ₃ O ₂ S ₂
291836	1-adamantyl	C ₁₅ H ₁₈ ClN ₃ O ₂ S ₂
291837	1-CO2Et-1-cyclopropyl	C ₁₁ H ₁₂ ClN ₃ O ₄ S ₂
291838	PhC(Me)2	C ₁₄ H ₁₄ ClN ₃ O ₂ S ₂
291839	1-(CH2OH)-1-cyclopentyl	C ₁₁ H ₁₄ ClN ₃ O ₃ S ₂
291840	1-CO2H-cyclopropyl	C ₉ H ₈ ClN ₃ O ₄ S ₂
291841	1-Me-1-cyclobutyl	C ₁₀ H ₁₂ ClN ₃ O ₂ S ₂
291842	1-Me-cyclohexyl	C ₁₂ H ₁₆ ClN ₃ O ₂ S ₂
291843	1-Me-cyclopentyl	C ₁₁ H ₁₄ ClN ₃ O ₂ S ₂
291844	1-Et-1-cyclobutyl	C ₁₁ H ₁₄ ClN ₃ O ₂ S ₂

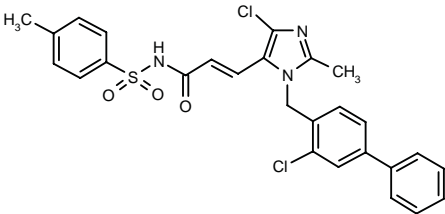
SOURCE – Novo Nordisk.

REFERENCES

1. Hansen, J.B. and Nielsen, F.E. (Novo Nordisk A/S) *Fused 1,2,4-thiadiazine derivs., their preparation and use.* WO 0037474.

292084

3-[4-Chloro-1-(3-chlorobiphenyl-4-ylmethyl)-2-methylimidazol-5-yl]-*N*-(4-methylphenylsulfonyl)-2(*E*)-propenamide



C27 H23 Cl2 N3 O3 S; Mol wt: 540.4687

ACTION – Hypoglycemic agent with cGMP-phosphodiesterase (cGMP-PDE)-inhibitory activity. In *db/db* mice, the compound decreased blood suger levels by 63% at 3.2 mg/kg p.o. Potentially useful for the treatment of diabetes, insulin resistance, impaired glucose tolerance and hyperglycemia, among others.

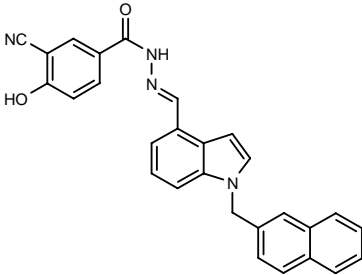
SOURCE – Fujisawa.

REFERENCES

1. Kayakiri, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Imidazole cpds. and medicinal use thereof.* WO 0039097.

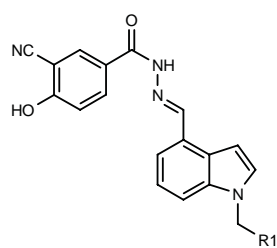
292217

3-Cyano-4-hydroxy-*N'*-[(*E*)-1-(2-naphthylmethyl)-1*H*-indol-4-ylmethylene]benzohydrazide



C28 H20 N4 O2; Mol wt: 444.4920

ACTION – Nonpeptide glucagon antagonist or inverse agonist, useful in the treatment of hyperglycemia associated with impaired glucose tolerance, insulin resistance, syndrome X, type 1 and type 2 diabetes, hyperlipidemia, dyslipidemia, hypertriglyceridemia, glucagonomas, acute pancreatitis, cardiovascular diseases, cardiac hypertrophy, gastrointestinal disorders, obesity-related diabetes, etc. It also may be used for increasing gastric acid secretion and for reversing glucagon-induced intestinal hypomotility and as a diagnostic agent. Other specifically claimed compounds include the following:



Compound	R1	Formula
292218	4-MeO-Ph	C ₂₈ H ₂₀ N ₄ O ₃
292219	2-Me-1-Naph	C ₂₉ H ₂₂ N ₄ O ₂
292220	2,4-(Me)2-Ph	C ₂₈ H ₂₂ N ₄ O ₂
292221	3,5-(Me)2-Ph	C ₂₈ H ₂₂ N ₄ O ₂
292222	2,3,5-(F)3-Ph	C ₂₄ H ₁₅ F ₃ N ₄ O ₂
292223	4-Br-Ph	C ₂₄ H ₁₇ BrN ₄ O ₂
292224	2,3,5,6-(Me)4-Ph	C ₂₈ H ₂₆ N ₄ O ₂

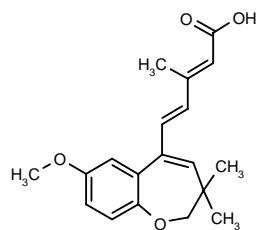
SOURCES – Agouron (Pfizer); Novo Nordisk.

REFERENCES

1. Ling, A. et al. (Novo Nordisk A/S;Agouron Pharmaceuticals, Inc.) *Glucagon antagonists/inverse agonists*. WO 0039088.

292314

5-(7-Methoxy-3,3-dimethyl-2,3-dihydro-1-benzoxepin-5-yl)-3-methyl-2(E),4(E)-pentadienoic acid



C19 H22 O4; Mol wt: 314.3788

ACTION – Activator of peroxisome proliferator-activated receptor PPAR α and PPAR γ isoforms, potentially useful for the treatment of dyslipidemias, atherosclerosis and diabetes.

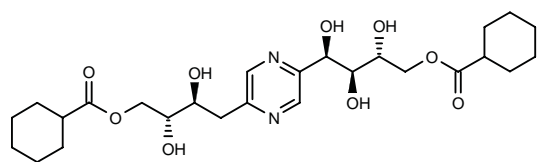
SOURCE – Merck KGaA.

REFERENCES

1. Brunet, M. et al. (Merck Patent GmbH) *Benzopyrans and benzoxepines, pharmaceutical compsns. comprising them and preparation process*. FR 2787789, WO 0039113.

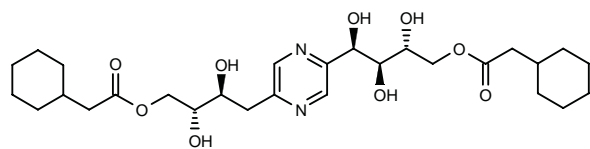
292508

Cyclohexanecarboxylic acid (2*R*,3*S*,4*R*)-4-[5-[(2*S*,3*R*)-4-(cyclohexylcarbonyloxy)-2,3-dihydroxybutyl]pyrazin-2-yl]-2,3,4-trihydroxybutyl ester



C26 H40 N2 O9; Mol wt: 524.6070

ACTION – Hypoglycemic agent with good activity and low toxicity in mice (LD₅₀ > 2000 mg/kg p.o.). Another exemplified polyhydroxypyrazine derivative is:



292509: C28 H44 N2 O9

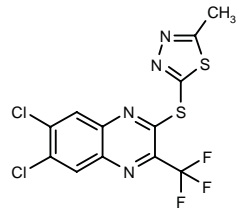
SOURCE – Aventis Pharma.

REFERENCES

1. Bouchard, H. and Commercon, A. (Aventis Pharma SA) *Novel polyhydroxypyrazine derivs., preparation and pharmaceutical compsns. containing same*. FR 2788274, WO 0042027.

292512

6,7-Dichloro-2-(5-methyl-1,3,4-thiadiazol-2-ylsulfanyl)-3-(trifluoromethyl)quinoxaline



C12 H5 Cl2 F3 N4 S2; Mol wt: 397.2315

ACTION – Glucagon-like peptide-1 (GLP-1) agonist with picomolar affinity for the cloned human GLP-1 receptor expressed in BHK cells (K_d = 120 pM). Potentially useful for the treatment or prevention of disorders where activation of the human GLP-1 receptor is beneficial, especially metabolic disorders such as impaired glucose tolerance, type 1 diabetes, type 2 diabetes and obesity.

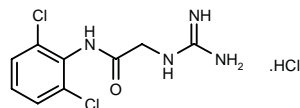
SOURCES – Agouron (Pfizer); Novo Nordisk.

REFERENCES

1. Teng, M. et al. (Novo Nordisk A/S;Agouron Pharmaceuticals, Inc.) *Non-peptide GLP-1 agonists*. WO 0042026.

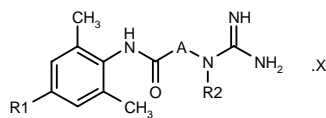
292601

N-(2,6-Dichlorophenyl)-2-guanidinoacetamide hydrochloride

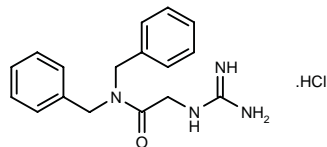


C9 H10 Cl2 N4 O . HCl; Mol wt: 297.5719

ACTION – Hypoglycemic agent proven to reduce glycemia by 9 and 14% on day 1 and by 13 and 27% on day 4, respectively, at doses of 20 and 200 mg/kg/day p.o. in non-insulin-dependent streptozotocin-diabetic rats. Potentially useful for the treatment of pathologies associated with insulin resistance syndrome such as diabetes, dyslipidemia, obesity, arterial hypertension, neuropathy, retinopathy and atherosclerosis. Compound is also reported to be useful to inhibit the formation of advanced glycosylation end products (AGEs). A representative compound from a series of [(aminoimino-methyl)amino]alkanecarboxamides, wherein the following are also included:



Compound	R1	R2	A	X	Formula
292602	H	H	-CH2-	H2SO4	C ₁₁ H ₁₆ N ₄ O .H ₂ O ₄ S
292603	H	H	-(CH2)2-		C ₁₂ H ₁₈ N ₄ O
292604	H	Me	-CH2-	HCl	C ₁₂ H ₁₈ N ₄ O.HCl
292605	H	H	-(S)-CH(Me)-	HCl	C ₁₂ H ₁₈ N ₄ O.HCl
292606	Me	H	-CH2-	HCl	C ₁₂ H ₁₈ N ₄ O.HCl
292607	H	H	-(S)-CH[CH(Me)Et]-	HCl	C ₁₅ H ₂₄ N ₄ O.HCl
292608	H	H	-(S)-CH(i-Bu)-	HCl	C ₁₅ H ₂₄ N ₄ O.HCl
292609	H	Me	-(S)-CH(i-Pr)-	HCl	C ₁₅ H ₂₄ N ₄ O.HCl



292610: C17 H20 N4 O . HCl

SOURCE – Merck KGaA.

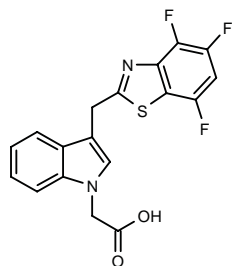
REFERENCES

1. Moinet, G. et al. (Merck Patent GmbH) *((Aminoiminomethyl)amino) alkanecarboxamides and their applications in therapy*. FR 2788275, WO 0042001.

TREATMENT OF DIABETIC COMPLICATIONS

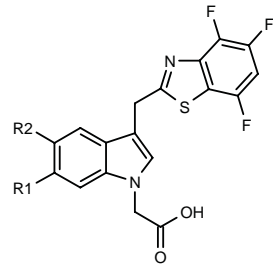
292696

3-(4,5,7-Trifluorobenzothiazol-2-ylmethyl)-1*H*-indole-1-acetic acid



C18 H11 F3 N2 O2 S; Mol wt: 376.3569

ACTION – Potent and selective aldose reductase (ALR) inhibitor with nanomolar potency against human ALR2 (IC₅₀ = 5 nM) and 5,400-fold less activity against human aldehyde reductase (ALR1; IC₅₀ = 27,000 nM). Potentially useful for the treatment of chronic diabetic complications. Other related substituted indolealkanoic acids include the following:



Compound	R1	R2	Formula
292697	H	Me	C ₁₉ H ₁₃ F ₃ N ₂ O ₂ S
292698	H	4-morpholinyl	C ₂₂ H ₁₈ F ₃ N ₃ O ₃ S
292699	OMe	H	C ₁₉ H ₁₃ F ₃ N ₂ O ₃ S
292700	Me	H	C ₁₉ H ₁₃ F ₃ N ₂ O ₂ S

SOURCE – Institute for Diabetes Discovery.

REFERENCES

1. Jones, M.L. et al. (The Institutes for Pharmaceutical Discovery, Inc.) *Substd. indolealkanoic acids*. WO 9950268.

2. Sredy, J. and Jacot, J. (The Institutes for Pharmaceutical Discovery, Inc.) *Methods of reducing serum glucose and triglyceride levels and for inhibiting angiogenesis using substd. indolealkanoic acids*. WO 0032180.

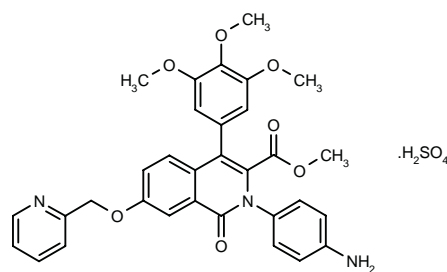
3. Jones, J.H. et al. *Substituted indolealkanoic acids as novel aldose reductase inhibitors*. 220th ACS Natl Meet (Aug 20-24, Washington) 2000, Abst MED1 307.

TREATMENT OF MALE SEXUAL DYSFUNCTION

T-1032

286867

2-(4-Aminophenyl)-1-oxo-7-(2-pyridinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester sulfate



C32 H29 N3 O7 . H2 O4 S; Mol wt: 665.6729

ACTION – Potent and selective phosphodiesterase type 5 (PDE5) inhibitor (IC_{50} = 0.001, 3, 10, 3, 0.03 and 100 μ M against PDE5, PDE1, PDE2, PDE4, PDE6 and PDE3, respectively) proven to concentration-dependently potentiate the relaxation induced by sodium nitroprusside in the canine corpus cavernosum precontracted with phenylephrine *in vitro*. In dogs, the intravenous (1-100 μ g/kg) and intraduodenal (3, 30 and 300 μ g/kg) administration of compound dose-dependently potentiated the penile tumescence induced by pelvic nerve stimulation, with comparable potency to sildenafil. In contrast, compound did not affect intracavernous pressure in the absence of pelvic nerve stimulation. Topical treatment with compound into the corpus cavernosum also potentiated the pelvic nerve stimulation-induced penile tumescence. In addition to potentiation of penile tumescence, compound showed potent and selective vasodilatory activity in dog pulmonary artery, increased venous capacity in anesthetized rats and increased cardiac output in dogs with heart failure induced by rapid ventricular pacing. Potentially useful for the treatment of male erectile dysfunction, as well as pulmonary hypertension and congestive heart failure.

SOURCE – Tanabe Seiyaku.

REFERENCES

1. Ukida, T. et al. (Tanabe Seiyaku Co., Ltd.) *Medicinal compsns.* JP 2000072675.
2. Ukita, T. et al. (Tanabe Seiyaku Co., Ltd.) *Isoquinolinone derivs., process for preparing the same, and their use as phosphodiesterase inhibitors.* JP 1998298164, WO 9838168.
3. Fujii, M. et al. *Prevention of cyclic GMP breakdown can enhance the effects of endogenous natriuretic peptides in heart failure.* Circulation 1999, 100(18, Suppl. 1): Abst 2313.
4. Inoue, H. et al. *T-1032, a new specific phosphodiesterase type V, increases venous capacity in anesthetized rats.* Jpn J Pharmacol 2000, 82(Suppl. 1): Abst P-384.
5. Nakamura, M. et al. *Synthesis of isoquinolone derivatives having specific PDE5 inhibitory effects.* 120th Annu Meet Pharm Soc Jpn (March 29-31, Gifu) 2000, Abst 30-PB-12-08.
6. Noto, T. et al. *A mechanism of the potentiation of penile tumescence by T-1032, a new potent and selective phosphodiesterase type V inhibitor, in dogs.* Jpn J Pharmacol 2000, 82(Suppl. 1): Abst P-385.
7. Noto, T. et al. *Potentiation of penile tumescence by T-1032, a new potent and specific phosphodiesterase type V inhibitor, in dogs.* J Pharmacol Exp Ther 2000, 294(3): 870.
8. Yano, K. et al. *Cardiovascular effects of T-1032, a novel and selective phosphodiesterase type V inhibitor, in normal and pulmonary hypertensive dogs.* Jpn J Pharmacol 2000, 82(Suppl. 1): Abst O-152.

TREATMENT OF GYNECOLOGICAL DISORDERS

EFLORNITHINE HYDROCHLORIDE*

Rec INNM; BAN; USAN

New indication

90024

2-Difluoromethyl-DL-ornithine monohydrochloride monohydrate

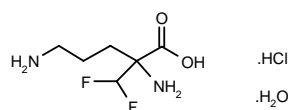
2-Difluoromethyl-2,5-diaminopentanoic acid monohydrochloride monohydrate

α -Difluoromethylornithine hydrochloride

DFMO

MDL-71782A

RMI-71782



C6 H12 F2 N2 O2 . HCl . H2O; Mol wt: 236.6445

ACTION – Putative irreversible inhibitor of skin ornithine decarboxylase activity.

INDICATION – Reduction of unwanted facial hair in women.

PRESENTATION – Cream containing 13.9% (139 mg/g) of anhydrous eflornithine hydrochloride as eflornithine hydrochloride monohydrate (150 mg/g).

PROPRIETARY NAME – Vaniqa (US).

SOURCES – Bristol-Myers Squibb; Gillette.

REFERENCES

1. *BMS and Gillette seek approval for Vaniqa in the U.S.* DailyDrugNews.com (Daily Essentials) 1999, Oct 7.
2. *Bristol-Myers Squibb updates investors at healthcare conference.* DailyDrugNews.com (Daily Essentials) 2000, Nov 3.
3. *First prescription drug to treat unwanted facial hair introduced in U.S.* DailyDrugNews.com (Daily Essentials) 2000, Oct 5.
4. *Vaniqa approved by FDA for women with unwanted facial hair.* DailyDrugNews.com (Daily Essentials) 2000, Aug 2.

*Eflornithine was originally developed at what is now Aventis as an antitrypanosomal (see Drug Data Rep 1992, 014(07): 0632), and is also in development at Ilex Oncology in collaboration with the National Cancer Institute for the treatment of bladder cancer.

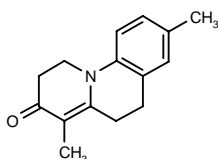
DERMATOLOGIC DRUGS

ACNE THERAPY

AS-601811*

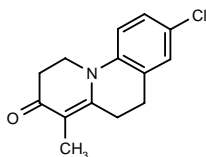
255960

4,8-Dimethyl-2,3,5,6-tetrahydro-1*H*-benzo[*c*]quinolizin-3-one



C₁₅ H₁₇ N O; Mol wt: 227.3090

ACTION – Potent, selective and reversible inhibitor of human steroid 5 α -reductase 1 (K_i = 2.7 nM against recombinant 5 α -R1 expressed in CHO cells) inactive against recombinant 5 α -R2 isoenzyme. Compound also displayed selective inhibitory activity against native 5 α -R1 enzyme in human scalp homogenates (IC_{50} = 41 nM) and was inactive (20% inhibition at 10 μ M) against native 5 α -R2 in human prostatic tissue. Suitable candidate for development of drugs for dihydrotestosterone-dependent skin disorders such as acne, male pattern baldness, androgenic alopecia in men and hirsutism in women. Another benzo[*c*]quinolizin-3-one inhibitor is:



AS-602240 [255959]**: C₁₄ H₁₄ Cl N O

SOURCES – Università degli Studi di Firenze, Firenze (IT); Serono.

REFERENCES

- Guarna, A. and Serio, M. (Applied Research Systems ARS Holdings NV) *Benzo[c]quinolizine derivs., their preparation and use as 5 α -reductases inhibitors*. EP 0880520, JP 2000504680, WO 9729107.
- Guarna, A. et al. *Benzo[c]quinolizin-3-ones: A novel class of potent and selective nonsteroidal inhibitors of human steroid 5 α -reductase 1*. J Med Chem 2000, 43(20): 3735.
- Guarna, A. et al. *Discovery of potent and selective inhibitors of human steroid 5 α -reductase 1, as drugs for androgen-dependent skin disorders*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-29.

*Identified compound **255960** (see **255009**) Drug Data Rep 1997, 019(11): 1005.

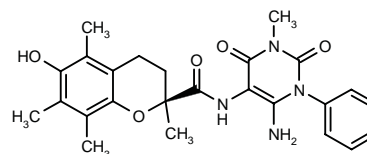
Identified compound **255959 (see **255009**) Drug Data Rep 1997, 019(11): 1005.

TREATMENT FOR ALLERGIC SKIN DISORDERS

CX-659S*

266921

N-(6-Amino-3-methyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2(*S*)-carboxamide



C₂₅ H₂₈ N₄ O₅; Mol wt: 464.5192

ACTION – Nonsteroidal antiallergic agent, an antioxidant giving an IC_{50} of 5.9 μ M against lipid peroxidation in rat brain homogenates, with potent cutaneous antiallergic activity after both oral and topical administration. In picryl chloride-induced contact hypersensitivity in mice, doses of 10 mg/kg p.o. or 0.03-0.3 mg/site induced significant inhibition of the delayed-type hypersensitivity reaction, without systemic toxicity after single or repeated administration.

SOURCE – Japan Energy.

REFERENCES

- Isobe, Y. et al. (Japan Energy Corp.) *Hydroquinone derivs. and their medicinal use*. JP 1998147575, US 5821247.
- Inoue, Y. et al. *Efficacy of CX-659S, a novel compound with an uracil skeleton, in an animal model of atopic dermatitis (1) - CX-659S shows activity similar to prednisolone*. Jpn J Allergol 1999, 48(8-9): 1098.
- Inoue, Y. et al. *Efficacy of CX-659S, a novel compound with an uracil skeleton, in an animal model of atopic dermatitis (2) - CX-659S inhibits prednisolone rebound*. Jpn J Allergol 1999, 48(8-9): 1098.
- Tobe, M. et al. *Synthesis and biological evaluation of CX-659S and its related compounds for their inhibitory effects on the delayed-type hypersensitivity reaction*. Bioorg Med Chem 2000, 8(8): 2037.

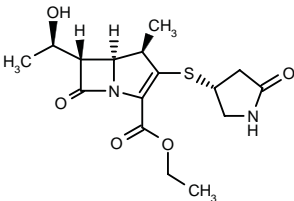
*Identified compound **266921** (see **265900**) Drug Data Rep 1998, 020(09): 0763.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

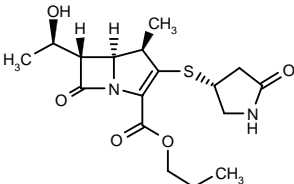
292506

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-[5-oxopyrrolidin-3(*R*)-ylsulfanyl]-1-methyl-1-carba-2-penem-3-carboxylic acid ethyl ester



C16 H22 N2 O5 S; Mol wt: 354.4248

ACTION – Carbapenem antibiotic with excellent anti-bacterial activity and oral absorption. In pharmacokinetic studies in dogs, the compound exhibited a C_{max} of 5.61 $\mu\text{g/ml}$, a t_{max} of 1.2 h, an $AUC_{(0-6)}$ of 15.06 $\mu\text{g.h/ml}$ and 58.8% bioavailability when administered orally at 10 mg/kg. Another exemplified compound is:



292507: C17 H24 N2 O5 S

SOURCE – Sankyo.

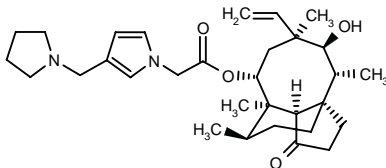
REFERENCES

1. Kawamoto, I. et al. (Sankyo Co., Ltd.) *Carbapenem ester cpds.* JP 2000264886, WO 0042041.

ANTIBACTERIAL DRUGS

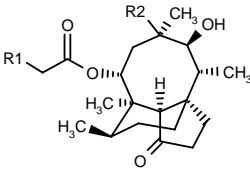
291792

2-[3-(1-Pyrrolidinylmethyl)-1*H*-pyrrol-1-yl]acetic acid (1*S*,2*R*,3*S*,4*S*,6*R*,7*R*,8*R*,14*R*)-3-hydroxy-2,4,7,14-tetra-methyl-9-oxo-4-vinyltricyclo[5.4.3.0^{1,8}]tetradec-6-yl ester



C31 H46 N2 O4; Mol wt: 510.7144

ACTION – Antibacterial mutilin active against *Staphylococcus aureus* Oxford and *Streptococcus pneumoniae*, with MIC values in the range 0.06-16 $\mu\text{g/ml}$. Other specifically claimed mutilin derivatives having a heteroaryl acetate substituent at the 14-position are:



Compound	R1	R2	Formula
291793	3-(NH2COCH2)-1-indolyl	vinyl	C ₃₂ H ₄₂ N ₂ O ₅
291794	3-(NH2CH2CH2)-1-indolyl	vinyl	C ₃₂ H ₄₄ N ₂ O ₄
291795	4-(1-Me-1,2,3,6-tetrahydro-4-Pyr)-1-pyrazolyl	vinyl	C ₃₁ H ₄₅ N ₃ O ₄
291796	5-(4-Pip)-1-pyrazolyl	vinyl	C ₃₀ H ₄₅ N ₃ O ₄
291797	3-(4-Pip)-1-pyrazolyl	vinyl	C ₃₀ H ₄₅ N ₃ O ₄
291798	4-(4-Pip)-1-pyrazolyl	Et	C ₃₀ H ₄₇ N ₃ O ₄
291799	3-[1-[2-N(Me2)-3,4-dioxo-1-cyclobutenyl]-4-Pip]-1-pyrazolyl	vinyl	C ₃₆ H ₅₀ N ₄ O ₆
291800	1-pyrazolyl	vinyl	C ₂₅ H ₃₆ N ₂ O ₄

SOURCE – SmithKline Beecham.

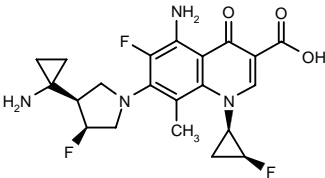
REFERENCES

1. Brooks, G. and Hunt, E. (SmithKline Beecham plc) *Mutillin 14-ester derivs. having antibacterial activity.* WO 0037074.

D61-1113*

271702

5-Amino-7-[3(*R*)-(1-aminocyclopropyl)-4(*S*)-fluoropyrrolidin-1-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C21 H23 F3 N4 O3; Mol wt: 436.4317

ACTION – Fluoroquinolone antibacterial with high potency against Gram-positive bacteria including *Staphylococcus aureus*, *Streptococcus pyogenes* and *Enterococcus faecalis* (MIC₅₀ = 0.008, 0.008 and 0.03 $\mu\text{g/ml}$, respectively), as well as against resistant strains such as methicillin-resistant *S. aureus* (MIC₅₀ = 0.03 $\mu\text{g/ml}$), methicillin- and ofloxacin-resistant *S. aureus* (MIC₅₀ = 0.06 $\mu\text{g/ml}$), methicillin-resistant coagulase-negative staphylococci (MIC₅₀ = 0.03 $\mu\text{g/ml}$), penicillin-resistant *Streptococcus pneumoniae* (MIC₅₀ = 0.015) and vancomycin-resistant *Enterococcus faecium* (MIC₅₀ = 0.25 $\mu\text{g/ml}$). Against resistant strains, compound was more potent than trovafloxacin, vancomycin, teicoplanin and linezolid. *In vivo*, compound protected against experimental mouse septicemia induced by vancomycin-resistant *E. faecalis* (ED₅₀ = 1.06 mg/kg i.v. vs. ED₅₀ > 100 mg/kg i.v. for vancomycin) and against rat endocarditis induced by methicillin-resistant *S. aureus*. Compound exhibited a favorable pharmacokinetic profile after i.v. administration in mice and rats, as well as after oral administration in

monkeys. A good safety profile was observed, with no acute toxicity (up to 200 mg/kg) after a single i.v. dose in mice, no repeated-dose toxicity in monkeys after 4 weeks' i.v. or p.o. administration (up to 50 and 30 mg/kg, respectively), no mutagenicity (up to 150 mg/kg i.v.) in mice (micronucleus test) and no convulsant activity in mice (up to 5 mg/kg). In addition, no phototoxicity, chondrotoxicity or cardiotoxicity was seen in mice (at a dose of 100 mg/kg i.v.), dogs (at a dose of 30 mg/kg i.v.) or isolated guinea pig myocardium (at a concentration of 100 µM), respectively.

SOURCE – Daiichi Pharmaceutical.

REFERENCES

1. Takemura, M. et al. (Daiichi Pharmaceutical Co., Ltd.) *cis-Disubst. aminocycloalkylpyrrolidine derivs.* EP 1020459, WO 9852939.

2. Takemura, M. et al. (Daiichi Pharmaceutical Co., Ltd.) *Subst. aminocycloalkylpyrrolidine derivs.* EP 0911328, WO 9719072.

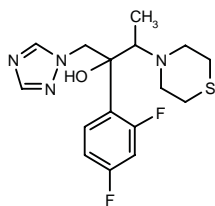
3. Takahashi, H. *Synthesis and biological evaluation of D61-1113, a novel fluoroquinolone having potent activity against Gram-positive bacteria including MRSA, PRSP and VRE.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1505.

*Identified compound **271702** Drug Data Rep 1999, 021(02): 0154.

ANTIFUNGAL AGENTS

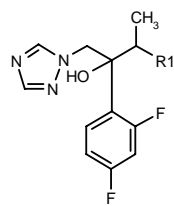
292065

2-(2,4-Difluorophenyl)-3-(4-thiomorpholinyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol



C16 H20 F2 N4 O S; Mol wt: 354.4230

ACTION – Potent antifungal agent shown to be more active than neticonazole against *Trychophyton mentagrophytes* and *Trichophyton rubrum* (MIC = 0.063 and 0.031 µg/ml, respectively, vs. 0.125 and 0.25 µg/ml, respectively, for neticonazole hydrochloride). Other exemplified azole derivatives include the following:



Compound	R1	Formula
292066	perhydro-1,4-thiazepin-4-yl	C ₁₇ H ₂₂ F ₂ N ₄ OS
292067	2-Me-4-thiomorpholinyl	C ₁₇ H ₂₂ F ₂ N ₄ OS

SOURCE – SSP.

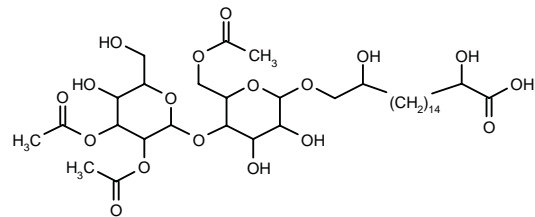
REFERENCES

1. Tokizawa, M. et al. (SSP Co., Ltd.) *Azole derivs. or their salts.* JP 2000169473.

AFB-8-A2

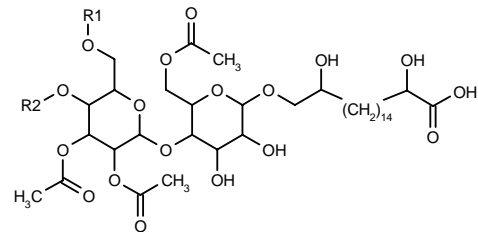
292073

18-[6-(Acetoxymethyl)-5-[3,4-diacetoxy-5-hydroxy-6-(hydroxymethyl)tetrahydropyran-2-yloxy]-3,4-dihydroxy-tetrahydropyran-2-yloxy]-2,17-dihydroxyoctadecanoic acid



C36 H62 O18; Mol wt: 782.8678

ACTION – Glycolipid isolated from a culture of *Cryptococcus* sp. IFO10934 (FERM BP-6581) and shown to exhibit antifungal activity against *Aspergillus fumigatus* and *Aspergillus niger in vitro* (MIC = 25 and 12.5 mg/ml, respectively) and against *A. fumigatus in vivo*, with 5 of 7 mice administered 50 mg/kg p.o. surviving up to day 10. Other compounds from the same source are:



Compound	R1	R2	Formula
AFB-8-A1 [292074]	H	Ac	C ₃₈ H ₆₄ O ₁₉
292075	Ac	H	C ₃₈ H ₆₄ O ₁₉

SOURCE – Takeda.

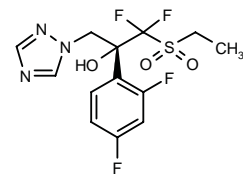
REFERENCES

1. Sakane, K. et al. (Takeda Chemical Industries, Ltd.) *Glycolipid, its preparation method and use.* JP 2000169495.

SS-750*

278842

(-)-2(*R*)-(2,4-Difluorophenyl)-1-(ethylsulfonyl)-1,1-difluoro-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol



C13 H13 F4 N3 O3 S; Mol wt: 367.3217

ACTION – Triazole antifungal agent with a broad antifungal spectrum against most pathogenic yeast including *Candida albicans*, *Candida krusei*, fluconazole-resistant *C. albicans*, *Candida glabrata* and *Cryptococcus neoformans* (MIC = 0.099, 0.871, 2.52, 0.445 and 1.055 µg/ml, respectively), and filamentous fungi including *Aspergillus flavus* and *Aspergillus fumigatus* (MIC = 1.782 and 2.00 µg/ml, respectively). In general, the *in vitro* antifungal activity of compound against the most pathogenic yeast and *Aspergillus* spp. was comparable to that of amphotericin B and was superior to that of fluconazole. *In vivo* in immunosuppressed mice, compound exhibited an excellent therapeutic effect by both p.o. and i.v. routes against systemic aspergillosis (ED₅₀ = 2.5 and 3.13 mg/kg/day for 7 days after p.o. and i.v. administration, respectively, in *A. fumigatus*-infected mice) and cryptococcosis (ED₅₀ = 2 mg/kg/day for 7 days after i.v. and p.o. administration in *C. neoformans*-infected mice). Other studies in immunosuppressed mice with systemic candidosis caused by *C. albicans* IFM 40009 demonstrated strong activity, with respective p.o. ED₅₀ values on days 7 and 14 after infection of 0.14 and 0.76 mg/kg/day versus 0.57 and 10.19 mg/kg/day, respectively, for fluconazole and 13.93 and > 64 mg/kg/day, respectively, for itraconazole. In mice with pulmonary candidosis caused by the same fungal strain, compound was more active than fluconazole and itraconazole (ED₅₀ = 0.66, 7.64 and > 64 mg/kg/day p.o. on day 14 after fungal infection, respectively). Results from studies on the absorption, distribution, metabolism and excretion of [¹⁴C]-SS-750, administered both i.v. and p.o., in rats demonstrated high absorption and high oral bioavailability (75.8%), as well as a long half-life (68.2 h after single oral dose). Suitable agent for both parenteral and oral dosing in the treatment of deep mycoses.

SOURCES – Aressa Pharmaceuticals; Nippon Kayaku; SSP.

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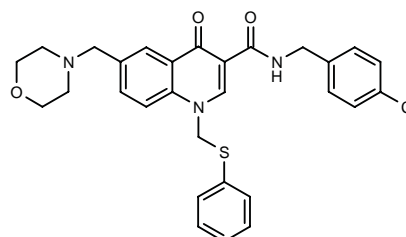
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2. Ishida, K. et al. *In vitro antifungal activity of SS750, a new triazole agent, and its effect on cytochrome P-450.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1081.
3. Kogure, T. et al. *Studies on the metabolic fate of SS750 in rats.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1082.
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6. Yokoyama, K. et al. *Therapeutic effect of SS750, a novel triazole antifungal agent, against systemic aspergillosis and cryptococcosis in mice.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1084.
7. *SSP and Nippon Kayaku codevelop antifungal triazole.* DailyDrugNews.com (Daily Essentials) 1999, Nov 19.
8. *SS750.* Arena Pharmaceuticals Web Site. December 13, 2000.

*Identified compound **278842** (see **278835**) Drug Data Rep 1999, 021(09): 0810.

ANTIVIRAL DRUGS

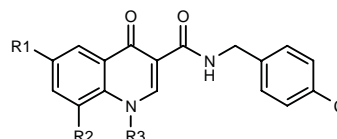
292416

N-(4-Chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-(phenylsulfanylmethyl)-1,4-dihydroquinoline-3-carboxamide



C₂₉ H₂₈ Cl N₃ O₃ S; Mol wt: 534.0772

ACTION – Antiviral agent particularly active against herpesviruses. The compound inhibited human cytomegalovirus, herpes simplex virus and varicella-zoster virus polymerase with IC₅₀ values of 0.18, < 0.31 and < 0.31 µM, respectively. Other exemplified quinoline-carboxamides include the following:



Compound	R1	R2	R3	Formula
292417	(CH ₂) ₃ OH	OCH ₂ CH ₂ OH	Me	C ₂₃ H ₂₅ ClN ₂ O ₅
292418	CH=CHCH ₂ OH	4-morpholinyl-CH ₂ CH ₂ O	Me	C ₂₇ H ₃₀ ClN ₃ O ₅
292419	(CH ₂) ₃ OH	H	cyclopropyl	C ₂₃ H ₂₃ ClN ₂ O ₃

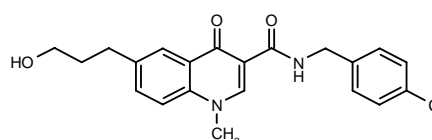
SOURCE – Pharmacia.

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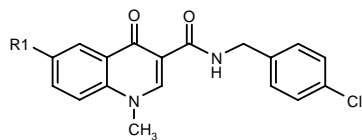
292420

N-(4-Chlorobenzyl)-6-(3-hydroxypropyl)-1-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide



C₂₁ H₂₁ Cl N₂ O₃; Mol wt: 384.8609

ACTION – Antiviral agent particularly active against herpesviruses. The compound inhibited human cytomegalovirus, herpes simplex virus and varicella-zoster virus polymerase with IC₅₀ values of 0.48, 0.32 and 0.41 μM, respectively. Other exemplified 4-oxo-1,4-dihydro-3-quinolinecarboxamides include the following:



Compound	R1	Formula
292421	C(Me)2CH2CH2OH	C ₂₃ H ₂₅ ClN ₂ O ₃
292422	4-morpholinyl-CH2	C ₂₃ H ₂₄ ClN ₃ O ₃

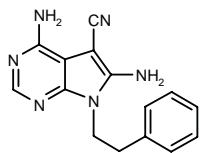
SOURCE – Pharmacia.

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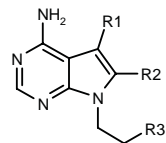
292518

4,6-Diamino-7-(2-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile



C15 H14 N6; Mol wt: 278.3176

ACTION – Non-nucleoside, nonphosphorylatable pyrrolo-[2,3-*d*]pyrimidine derivative with good antiviral activity and acceptable cytotoxicity, particularly active against human cytomegalovirus (HCMV) and herpes simplex virus type 1 (HSV-1). Other exemplified compounds within this series include the following:



Compound	R1	R2	R3	Formula
292519	CN	H	Ph	C ₁₅ H ₁₃ N ₅
292520	CSNH2	H	Ph	C ₁₅ H ₁₅ N ₅ S
292521	CN	Br	Ph	C ₁₅ H ₁₂ BrN ₅
292522	CN	NH2	CH2Ph	C ₁₆ H ₁₆ N ₆
292523	CSNH2	H	CH2Ph	C ₁₆ H ₁₇ N ₅ S

SOURCE – University of Michigan, Ann Arbor, MI (US).

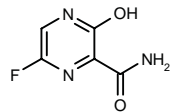
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T-705*

286877

6-Fluoro-3-hydroxypyrazine-2-carboxamide



C5 H4 F N3 O2; Mol wt: 157.1036

ACTION – Antiviral agent active against influenza virus A, B and C (IC₅₀ = 0.02-0.6 μg/ml) including neuraminidase inhibitor GS-4071-resistant strains (IC₉₀ = 0.095 μg/ml). Compound exhibited high selectivity for influenza virus against other viruses including human cytomegalovirus, herpes simplex virus type 1 and adenovirus (IC₅₀ > 100 μg/ml), as well as poliomyelitis virus, rhinoviruses and respiratory syncytial virus (IC₅₀ = 9.1, 27 and 35 μg/ml, respectively). No cytotoxicity was reported for compound against MDCK, Vero, HEL and L-132 cells (CC₅₀ > 1000 μg/ml). Compound was found to inhibit the viral replication stage but not the fusion or uncoating stage, and it exhibited virucidal activity. *In vivo*, oral compound completely prevented the death of mice receiving a high viral (influenza A/PR/8/34 virus) challenge dose, when administered both simultaneously to viral infection or 24 h postinfection. The therapeutic efficacy of compound at 50 and 100 mg/kg/day p.o. for 5 days was superior to that of oseltamivir. Moreover, compound significantly alleviated the symptoms of infection and reduced virus titers in ferrets inoculated intranasally with influenza A/PR/8/34 virus. Potentially useful for the treatment of influenza virus infections.

SOURCE – Toyama.

REFERENCES

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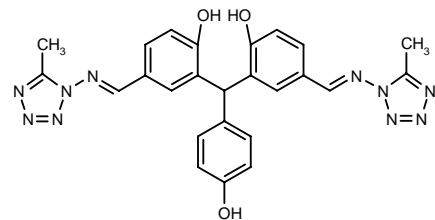
2. Furuta, Y. et al. In vitro and in vivo activities of antiviral compound T-705 against influenza virus. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1852.

*Identified compound **286877** (see **286833**) Drug Data Rep 2000, 022(06): 0537.

VP-14637

276028

2,2'-(4-Hydroxybenzylidene)bis[4-(5-methyl-1H-tetrazol-1-yliminomethyl)phenol]



C25 H22 N10 O3; Mol wt: 510.5158

ACTION – Antiviral agent, a potent and selective inhibitor of respiratory syncytial virus (RSV) replication in cell culture, with IC₅₀ values ranging from 0.1 nM to 80 nM against clinical isolates of RSV. The mechanism by which compound inhibits RSV replication involves functions associated with the viral F (fusion) protein. It recently entered clinical trials.

SOURCE – ViroPharma.

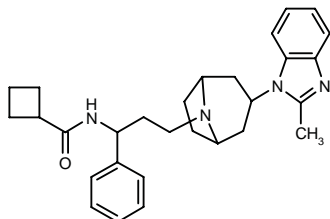
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5. *Clinical trials of new RSV therapeutic VP-14637 commence*. DailyDrugNews.com (Daily Essentials) 2000, Dec 30.
6. *ViroPharma to advance new anti-RSV candidate to clinical trials*. DailyDrugNews.com (Daily Essentials) 1999, May 26.

AIDS MEDICINES

291730

N-[3-[3-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]-1-phenylpropyl]cyclobutanecarboxamide



C29 H36 N4 O; Mol wt: 456.6304

ACTION – A representative compound from a series of azabicycloalkanes that acts as a modulator of the chemokine CCR5 receptor. The compound may be useful for the treatment of inflammatory diseases and for the therapy or prevention of HIV and genetically related retroviral infections.

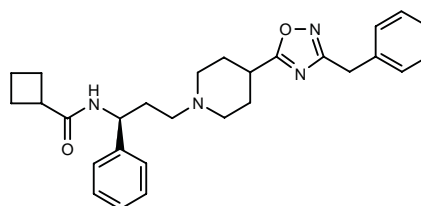
SOURCE – Pfizer.

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1. Armour, D.R. et al. (Pfizer Ltd.;Pfizer Inc.) *Azabicycloalkanes as CCR5 modulators*. WO 0038680.

291731

N-[3-[4-(3-Benzyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-1(*S*)-phenylpropyl]cyclobutanecarboxamide



C28 H34 N4 O2; Mol wt: 458.6026

ACTION – A representative compound from a series of piperidines that acts as a modulator of the chemokine CCR5 receptor. The compound may be useful for the treatment of inflammatory diseases and for the therapy or prevention of HIV and genetically related retroviral infections.

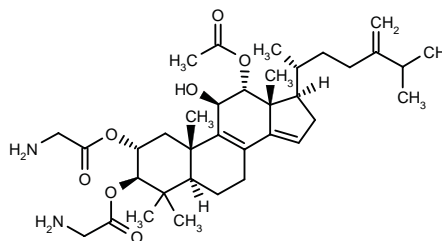
SOURCE – Pfizer.

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1. Armour, D.R. et al. (Pfizer Ltd.;Pfizer Inc.) *Piperidines as CCR5 modulators*. WO 0039125.

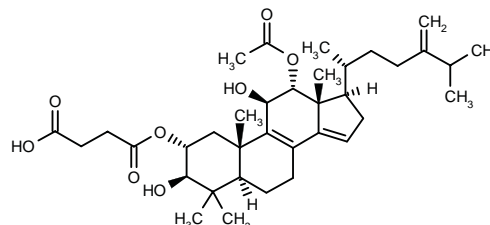
291737

12 α -Acetoxy-2 α ,3 β -bis(2-aminoacetoxy)-4,4-dimethyl-24-methylene-5 α -cholesta-8,14-dien-11 β -ol



C36 H56 N2 O7; Mol wt: 628.8454

ACTION – Potent HIV integrase inhibitor (IC₅₀ = 5 μ M in an assay for the strand transfer activity of recombinant HIV integrase) isolated from the aerobic fermentation of the fungus *Fusarium* sp. MF 6381 (ATCC 74469). Another compound from this source is:



291738: C36 H54 O8

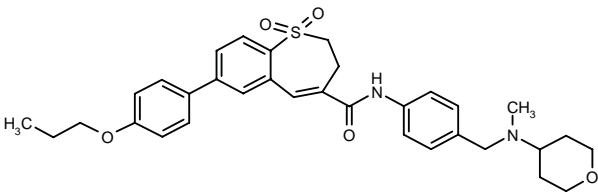
SOURCE – Merck & Co.

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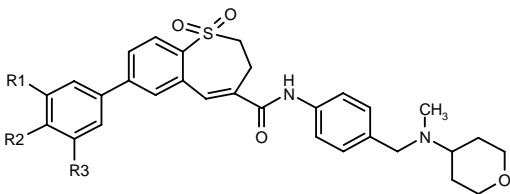
291991

N-[4-[*N*-Methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-7-(4-propoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide



C33 H38 N2 O5 S; Mol wt: 574.7382

ACTION – Antiviral agent that acts as an antagonist of the chemokine CCR5 receptor and is potentially useful for the treatment or prevention of HIV infection and AIDS. Other specifically claimed benzothiepinanilide derivatives include the following:



Compound	R1	R2	R3	Formula
291992	H	N(Me)CH2CH2OPr	H	C ₃₆ H ₄₅ N ₃ O ₅ S
291993	H	OCH2CH2OPr	H	C ₃₅ H ₄₂ N ₂ O ₆ S
291994	Me	OCH2CH2OEt	Me	C ₃₈ H ₄₄ N ₂ O ₆ S
291995	H	OPr	Me	C ₃₄ H ₄₀ N ₂ O ₅ S

SOURCE – Takeda.

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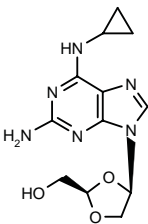
1. Shiraishi, M. et al. (Takeda Chemical Industries, Ltd.) *Benzothiepin-anilide derivs., their production and their use for antagonizing CCR-5*. WO 0037455.

292083

(–)-(2*R*,4*R*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-1,3-dioxolane-2-methanol

(–)-(2*R*,4*R*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-(hydroxymethyl)-1,3-dioxolane

*N*⁶-Cyclopropyl-9-[2(*R*)-(hydroxymethyl)-1,3-dioxolan-4(*R*)-yl]purine-2,6-diamine



C12 H16 N6 O3; Mol wt: 292.2974

ACTION – Antiviral agent, a purine nucleoside analogue that demonstrates potent antiretroviral activity against HIV-1 in various cell lines, being similar to approved anti-HIV drugs, as well as improved bioavailability and pharmacokinetic properties. It can be administered in combination with reverse transcriptase inhibitors or protease inhibitors and is potentially useful in the treatment of HIV and HBV infection.

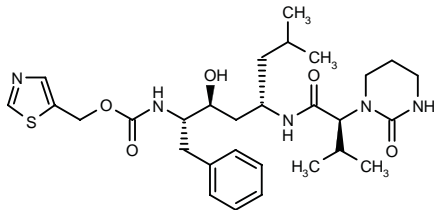
SOURCE – BioChem Pharma.

REFERENCES

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292354

N-[1(*S*)-Benzyl-2(*S*)-hydroxy-6-methyl-4(*S*)-[3-methyl-2(*S*)-(2-oxohexahydropyrimidin-1-yl)butyramido]-heptyl]carbamic acid thiazol-5-ylmethyl ester



C29 H43 N5 O5 S; Mol wt: 573.7547

ACTION – Aspartic protease inhibitor, particularly active against HIV-1 protease (*K_i* = 70 ± 10 pM), proven to have excellent potency against HIV-1 with an *EC*₅₀ of 0.5 μM in an HIV antiviral assay, while being nontoxic to normal cells (*IC*₅₀ > 100 μM). The compound exhibited an oral bio-availability of 100% and a *C*_{max} of 24.8 μM when tested in i.v.–p.o. crossover studies in rats.

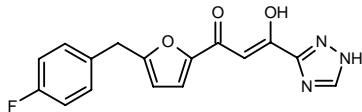
SOURCE – US Department of Health & Human Services (US).

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292402

1-[5-(4-Fluorobenzyl)furan-2-yl]-3-hydroxy-3-(1*H*-1,2,4-triazol-3-yl)-2(*Z*)-propen-1-one



C16 H12 F N3 O3; Mol wt: 313.2868

ACTION – A representative compound from a series of aromatic heterocyclic compounds with HIV integrase-inhibitory activity. The compound exhibited an *IC*₅₀ value of 0.53 μg/ml for inhibition of HIV-1 integrase and was active *in vitro* against HIV-1 and HIV-2 with respective *EC*₅₀ values of 57 and 35 ng/ml.

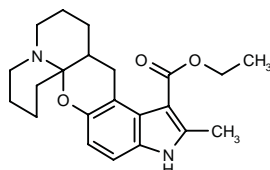
SOURCE – Shionogi.

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1. Fujishita, T. et al. (Shionogi & Co. Ltd.) *Aromatic heterocycle cpds. having HIV integrase inhibiting activities*. WO 0039086.

292449

2-Methyl-3,7,8,9,10,12,13,14,14a,15-decahydropyrrolo-[3',2':5,6][1]benzopyrano[3,2-*l*]quinolizine-1-carboxylic acid ethyl ester



C22 H28 N2 O3; Mol wt: 368.4742

ACTION – Chemokine receptor modulator acting preferably at the CCR5 receptor, found to block the binding of sCD4/gp120 to CCR5 receptors. Potentially useful for the prevention or treatment of HIV infection, delaying the onset of AIDS, or for the treatment of AIDS. Its use in the therapy of inflammatory diseases is also specifically claimed.

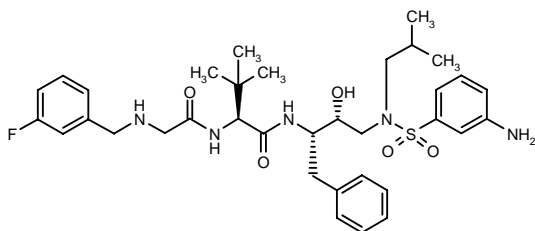
SOURCE – Pfizer.

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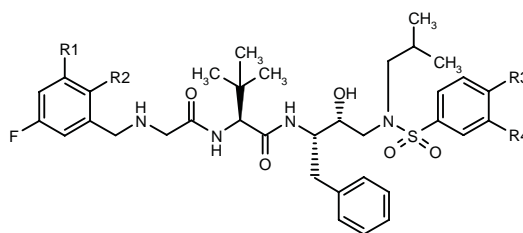
292582

N-[3-[*N*-(3-Aminophenylsulfonyl)-*N*-isobutylamino]-1(*S*)-benzyl-2(*R*)-hydroxypropyl]-2(*S*)-[2-(3-fluorobenzyl-amino)acetamido]-3,3-dimethylbutyramide



C35 H48 F N5 O5 S; Mol wt: 669.8582

ACTION – Antiviral agent, an HIV protease inhibitor useful for the treatment of HIV infection alone or in combination with HIV reverse transcriptase inhibitors or other HIV protease inhibitors. Other specifically claimed bis-amino acid sulfonamides containing substituted benzylamines are:



Compound	R1	R2	R3	R4	Formula
292583	H	H	NH2	H	C ₃₅ H ₄₈ FN ₅ O ₅ S
292584	F	H	H	NH2	C ₃₅ H ₄₇ F ₂ N ₅ O ₅ S
292585	F	H	NH2	H	C ₃₅ H ₄₇ F ₂ N ₅ O ₅ S
292586	H	F	H	NH2	C ₃₅ H ₄₇ F ₂ N ₅ O ₅ S
292587	H	F	NH2	H	C ₃₅ H ₄₇ F ₂ N ₅ O ₅ S

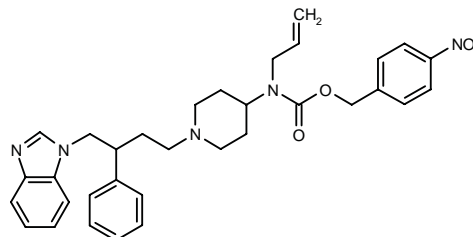
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Kaltenbach, R.F. and Trainor, G.L. (DuPont Pharmaceuticals Co.) *Bis-amino acid sulfonamides containing N-terminally A substd. benzyl group as HIV protease inhibitors*. WO 0042060.

292657

N-Allyl-*N*-[1-[4-(1*H*-benzimidazol-1-yl)-3-phenylbutyl]-piperidin-4-yl]carbamic acid 4-nitrobenzyl ester



C33 H37 N5 O4; Mol wt: 567.6863

ACTION – Chemokine CCR5 receptor antagonist with nanomolar binding affinity for the receptor (IC₅₀ = 4 nM) and the ability to block the entry of M-tropic HIV-1 strains into host cells *in vitro* (CIC₉₀ = 1000 nM in HeLa cell viral spread assay). Compound exhibited an oral bioavailability of 14% in rats.

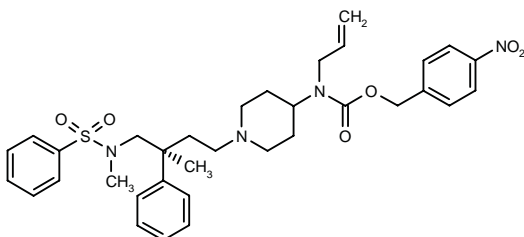
SOURCE – Merck & Co.

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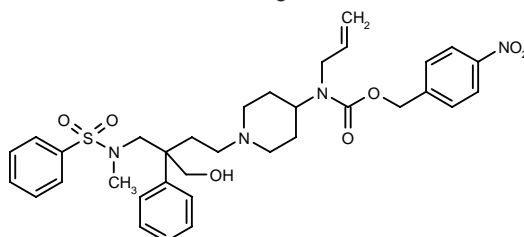
292693

1-[3(*S*)-Methyl-4-[*N*-methyl-*N*-(phenylsulfonyl)amino]-3-phenylbutyl]piperidin-4-yl-*N*-(2-propenyl)carbamic acid 4-nitrobenzyl ester



C34 H42 N4 O6 S; Mol wt: 634.7938

ACTION – Potent, small-molecule chemokine CCR5 receptor antagonist ($IC_{50} = 1$ nM) with 300-1,000-fold selectivity over other chemokine and neurokinin receptors, although undesirable activities were detected in ion channel and G-protein-linked receptor assays. Compound exhibited potent anti-HIV activity in HIV-infected human peripheral blood mononuclear cells ($IC_{95} = 8$ nM or less), as well as in HeLa cells expressing both human CXCR4 and CCR5 receptors ($IC_{90} = 3$ nM). Following i.v. dosing at 2 mg/kg, compound showed 29% oral bioavailability and a serum half-life of 2 h in rats, but < 1% oral bioavailability and a half-life of 10 h in dogs. Another potent chemokine CCR5 antagonist is:



292694: C34 H42 N4 O7 S

SOURCE – Merck & Co.

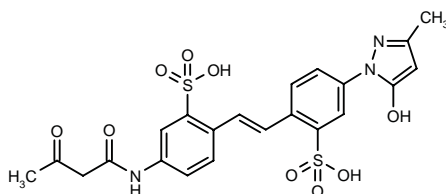
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CGA-137053**291608**

(*E*)-4-(2-Acetylacetamido)-4'-(5-hydroxy-3-methyl-1*H*-pyrazol-1-yl)stilbene-2,2'-disulfonic acid



C22 H21 N3 O9 S2; Mol wt: 535.5519

ACTION – Anti-HIV-1 agent that specifically blocks intracellular Tat/TAR complexation and prevents HIV-1 gene activation, while showing no affinity for TAR RNA.

Compound suppressed the Tat-driven induction of CXCR4 coreceptor expression in human peripheral blood lymphocytes (PBLs), where it showed concentration-dependent inhibition of HIV-1 replication, with complete suppression at a concentration of 30 μ M. Almost complete suppression of viral replication was also seen at 30 μ M in differentiated macrophages, and antiviral activity against various strains of HIV-1, HIV-2 and SIV was observed, with EC_{90} values of 0.5-5 μ M. No cytotoxicity was seen in any of the cells tested at up to 100 μ M.

SOURCE – Novartis.

REFERENCES

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2. Klimkait, T. et al. *Tat protein as target: A new inhibitor-concept for HIV*. 13th Int AIDS Conf (July 9-14, Durban) 2000, Abst WeOrA537.

LOPINAVIR/RITONAVIR**291602**

Lopinavir coformulated with a small amount of ritonavir

ABT-378/r

ABT-378/ritonavir

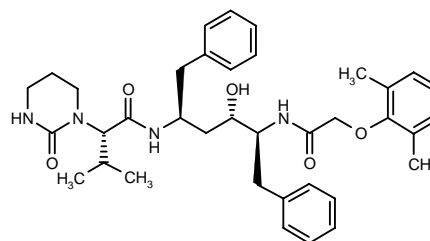
Lopinavir

Prop INN; USAN

246659

N-[1(*S*)-Benzyl-3(*S*)-hydroxy-4(*S*)-[2-(2,6-dimethylphenyl)acetamido]-5-phenylpentyl]-3-methyl-2(*S*)-(2-oxo-hexahydropyrimidin-1-yl)butyramide

ABT-378⁺



C37 H48 N4 O9; Mol wt: 628.8190

Ritonavir⁺⁺

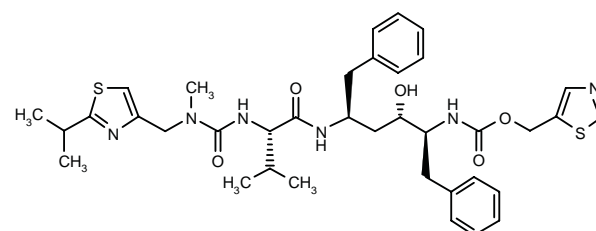
Prop INN; USAN

207282

N-[*N*-(2-Isopropylthiazol-4-ylmethyl)-*N*-methylcarbamoyl]-L-valine 1(*S*)-benzyl-3(*S*)-hydroxy-5-phenyl-4(*S*)-(thiazol-5-ymethoxycarbonylamino)pentylamide

ABT-538

Norvir[®]



C37 H48 N6 O5 S2; Mol wt: 720.9600

ACTION – A coformulation of the HIV protease inhibitors lopinavir and ritonavir; the latter acts as an inhibitor of the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of the drug.

INDICATION – Treatment of HIV infection in adults and children 6 months of age and older in combination with other antiretroviral medications.

PRESENTATION – Capsules, 133.3 mg lopinavir and 33.3 mg ritonavir; oral solution (5 ml), 400 mg lopinavir and 100 mg ritonavir (80 mg lopinavir/20 mg ritonavir per ml).

PROPRIETARY NAME – Kaletra (US).

SOURCE – Abbott.

RECENT REFERENCES

1. Becker, S. et al. *ABT-378/ritonavir (ABT-378/r) and efavirenz: 24 Week safety/efficacy evaluation in multiple PI experienced patients.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst I-697.

2. Benson, C. et al. *ABT-378/ritonavir (ABT-378/r) in protease inhibitor-experienced HIV-infected patients: Preliminary 24 week results.* Antivir Ther 1999, 4(Suppl. 1): Abst 7.

3. Benson, C. et al. *Two year follow-up of ABT-378/ritonavir (ABT-378/r) in antiretroviral naïve HIV+ patients.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst I-546.

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5. Bertz, R. et al. *Multiple-dose pharmacokinetics (PK) of ABT-378/ritonavir (ABT-378/r) in HIV+ subjects.* 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst A327.

6. Brun, S. et al. *Analysis of viral isolates following viral load rebound on therapy with ABT-378/ritonavir (ABT-378/r).* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst I-2112.

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8. Clumek, N. et al. *ABT-378/ritonavir (ABT-378/r) and efavirenz: 16 Week safety/efficacy evaluation in multiple PI experienced patients.* 13th Int AIDS Conf (July 9-14, Durban) 2000, Abst TuPeB3196.

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10. Eron, J. et al. *ABT-378/ritonavir (ABT-378/r) suppresses HIV RNA < 400 copies/mL in 95% of treatment-naïve patients and in 78% of PI-experienced patients at 36 weeks.* 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst LB-20.

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12. Gustavson, L. et al. *Assessment of the bioequivalence and food effects for liquid and soft elastic capsules co-formulations of ABT-378/ritonavir (ABT-378/r) in healthy subjects.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst I-1659.

13. Hicks, C. et al. *ABT-378/ritonavir (ABT-378/R) in antiretroviral naïve HIV + patients 48 weeks.* 7th Eur Conf Clin Aspects Treat HIV Infect (Oct 23-27, Lisbon) 1999, Abst 585.

14. Hsu, A. et al. *Trough concentrations-EC50 relationship as a predictor of viral response for ABT-378/ritonavir (ABT-378/r) in treatment-experienced patients.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst I-1660.

15. Kempf, D. et al. *Analysis of virological response to ABT-378/ritonavir therapy in protease inhibitor-experienced patients with respect to baseline viral phenotype and genotype.* Antivir Ther 1999, 4(Suppl. 1): Abst 8.

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17. Kempf, D. et al. *Identification of clinically relevant phenotypic and genotypic breakpoints for ABT-378/r in multiple PI-experienced; NNRTI-naïve patients.* Antivir Ther 2000, 5(Suppl. 3): Abst 89.

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19. Kessler, H. et al. *Analysis of safety data from ABT-378/ritonavir (ABT-378/r) in two phase II clinical trials.* 13th Int AIDS Conf (July 9-14, Durban) 2000, Abst TuPeB3198.

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24. Petrossian, V.D. et al. *Development of a palatable, oral solution containing lopinavir (ABT-378) and ritonavir.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3020.

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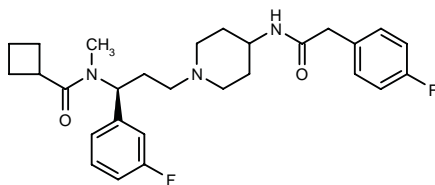
+Drug Data Rep 1997, 019(07): 0642.

++Drug Data Rep 1996, 018(05): 0456.

UK-386739

291729

N-[1(S)-(3-Fluorophenyl)-3-[4-[2-(4-fluorophenyl)acetamido]piperidin-1-yl]propyl]-N-methylcyclobutanecarboxamide



C28 H35 F2 N3 O2; Mol wt: 483.5995

ACTION – A representative compound from a series of aminoazacycloalkanes that acts as a modulator of the chemokine CCR5 receptor. The compound may be useful for the treatment of inflammatory diseases and for the therapy or prevention of HIV and genetically related retroviral infections.

SOURCE – Pfizer.

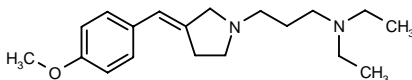
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TREATMENT OF PROTOZOAL DISEASES

292577

N,N-Diethyl-3-[3-(4-methoxybenzylidene)pyrrolidin-1-yl]-propan-1-amine



C19 H30 N2 O; Mol wt: 302.4590

Oil.

ACTION – Chloroquine resistance-reversing agent proven able to eliminate parasitemia when administered in combination with chloroquine in mice infected with chloroquine-resistant *Plasmodium yoelii nigeriensis*. Compound inhibited heme oxygenase activity of cell-free *P. yoelii nigeriensis* to a greater extent than enzyme from host (infected mice) blood (87 and 31%, respectively, at 100 μ M) and it completely inhibited heme oxygenase and glutathione-*S*-transferase activity in *P. yoelii nigeriensis* isolated from infected mice treated orally with compound.

SOURCE – Central Drug Research Institute, Lucknow (IN).

REFERENCES

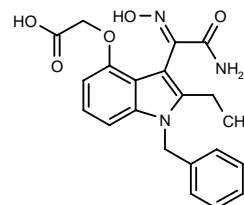
1. Batra, S. et al. *A new class of potential chloroquine-resistance reversal agents for plasmodia: Syntheses and biological evaluation of 1-(3'-diethylaminopropyl)-3-(substituted phenylmethylene)pyrrolidines*. J Med Chem 2000, 43(18): 3428.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

291740

2-[3-[2-Amino-1-(hydroxyimino)-2-oxoethyl]-1-benzyl-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid



C21 H21 N3 O5; Mol wt: 395.4129

ACTION – Potent and selective inhibitor of secretory phospholipase A₂ (sPLA₂; IC₅₀ = 49 nM for inhibition of recombinant human sPLA₂ in a chromogenic assay), potentially useful for the treatment of inflammatory diseases.

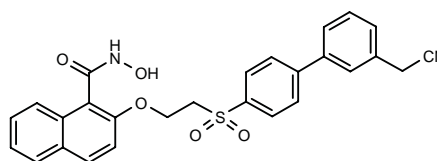
SOURCE – Lilly.

REFERENCES

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291848

2-[2-[3'-(Cyanomethyl)biphenyl-4-ylsulfonyl]ethoxy]naphthalene-1-carboxylic acid



C27 H22 N2 O5 S; Mol wt: 486.5458

ACTION – Matrix metalloproteinase (MMP) inhibitor that inhibits stromelysin (MMP-3) with an IC₅₀ value of 0.062 μ M. This compound is potentially useful for the treatment of tissue degradation diseases including rheumatoid arthritis, osteoarthritis, osteoporosis and neoplastic diseases. Other exemplified *N*-hydroxynaphthalene-1-carboxamides include the following:

ACTION – A representative compound from a series of aminoazacycloalkanes that acts as a modulator of the chemokine CCR5 receptor. The compound may be useful for the treatment of inflammatory diseases and for the therapy or prevention of HIV and genetically related retroviral infections.

SOURCE – Pfizer.

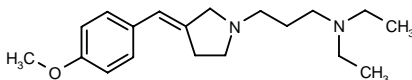
REFERENCES

1. Armour, D.R. et al. (Pfizer Inc.;Pfizer Ltd.) *Aminoazacycloalkanes as CCR5 modulators*. EP 1013276, JP 2000212159.

TREATMENT OF PROTOZOAL DISEASES

292577

N,N-Diethyl-3-[3-(4-methoxybenzylidene)pyrrolidin-1-yl]-propan-1-amine



C19 H30 N2 O; Mol wt: 302.4590

Oil.

ACTION – Chloroquine resistance-reversing agent proven able to eliminate parasitemia when administered in combination with chloroquine in mice infected with chloroquine-resistant *Plasmodium yoelii nigeriensis*. Compound inhibited heme oxygenase activity of cell-free *P. yoelii nigeriensis* to a greater extent than enzyme from host (infected mice) blood (87 and 31%, respectively, at 100 μ M) and it completely inhibited heme oxygenase and glutathione-*S*-transferase activity in *P. yoelii nigeriensis* isolated from infected mice treated orally with compound.

SOURCE – Central Drug Research Institute, Lucknow (IN).

REFERENCES

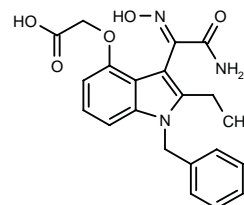
1. Batra, S. et al. *A new class of potential chloroquine-resistance reversal agents for plasmodia: Syntheses and biological evaluation of 1-(3'-diethylaminopropyl)-3-(substituted phenylmethylene)pyrrolidines*. J Med Chem 2000, 43(18): 3428.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

291740

2-[3-[2-Amino-1-(hydroxyimino)-2-oxoethyl]-1-benzyl-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid



C21 H21 N3 O5; Mol wt: 395.4129

ACTION – Potent and selective inhibitor of secretory phospholipase A₂ (sPLA₂; IC₅₀ = 49 nM for inhibition of recombinant human sPLA₂ in a chromogenic assay), potentially useful for the treatment of inflammatory diseases.

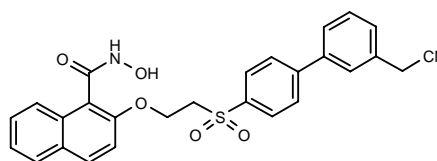
SOURCE – Lilly.

REFERENCES

1. Bach, N.J. et al. (Eli Lilly and Company) *Novel sPLA₂ inhibitors*. WO 0037358.

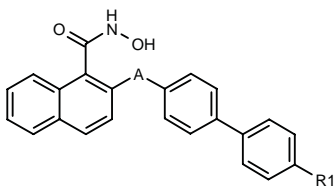
291848

2-[2-[3'-(Cyanomethyl)biphenyl-4-ylsulfonyl]ethoxy]naphthalene-1-carboxylic acid



C27 H22 N2 O5 S; Mol wt: 486.5458

ACTION – Matrix metalloproteinase (MMP) inhibitor that inhibits stromelysin (MMP-3) with an IC₅₀ value of 0.062 μ M. This compound is potentially useful for the treatment of tissue degradation diseases including rheumatoid arthritis, osteoarthritis, osteoporosis and neoplastic diseases. Other exemplified *N*-hydroxynaphthalene-1-carboxamides include the following:



Compound	R1	A	Formula
291849	Cl	-CH2CH2O-	C ₂₅ H ₂₀ ClNO ₃
291850	Cl	-OCH2CH2SO2-	C ₂₅ H ₂₀ ClNO ₅ S
291851	OMe	-OCH2CH2SO2-	C ₂₆ H ₂₃ NO ₆ S
291852	Cl	-CH2CH2SO2-	C ₂₅ H ₂₀ ClNO ₄ S
291853	OCF3	-CH2NHSO2-	C ₂₅ H ₁₉ F ₃ N ₂ O ₅ S
291854	OMe	-(CH2)3SO2-	C ₂₇ H ₂₅ NO ₅ S
291855	OMe	-(CH2)3CO-	C ₂₈ H ₂₅ NO ₄
291856	OMe	-CH2CH2CO-	C ₂₇ H ₂₃ NO ₄

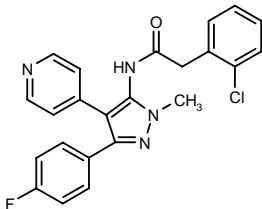
SOURCE – Abbott.

REFERENCES

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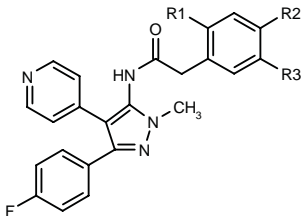
292245

2-(2-Chlorophenyl)-N-[3-(4-fluorophenyl)-1-methyl-4-(4-pyridinyl)-1H-pyrazol-5-yl]acetamide



C23 H18 Cl F N4 O; Mol wt: 420.8732

ACTION – Potent p38 MAP kinase inhibitor (IC₅₀ = 0.0088 pM), potentially useful for the treatment of diseases mediated by TNF-α, IL-1, IL-6 or COX-2 such as arthritis, psoriatic arthritis, inflammatory bowel disease, Crohn’s disease, multiple sclerosis, septic and endotoxic shock, etc. Other exemplified aminopyrazole derivatives include the following:



Compound	R1	R2	R3	Formula
292246	F	F	H	C ₂₃ H ₁₇ F ₃ N ₄ O
292247	Me	H	Me	C ₂₆ H ₂₃ FN ₄ O
292248	Br	H	H	C ₂₃ H ₁₈ BrFN ₄ O
292249	OMe	H	H	C ₂₄ H ₂₁ FN ₄ O ₂

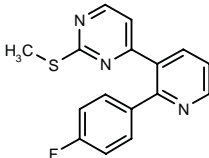
SOURCE – Teikoku Hormone.

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1. Minami, N. et al. (Teikoku Hormone Manufacturing Co., Ltd.) *Aminopyrazole derivs*. WO 0039116.

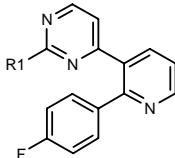
292368

4-[2-(4-Fluorophenyl)pyridin-3-yl]-2-(methylsulfanyl)-pyrimidine



C16 H12 F N3 S; Mol wt: 297.3558

ACTION – CSBP/RK/p38 kinase inhibitor (IC₅₀ < 50 μM) that inhibits the production of cytokines including IL-1, IL-6, IL-8 and TNF. The compound is potentially useful for the treatment of cytokine-mediated disorders such as arthritic conditions, sepsis, septic shock, stroke, asthma, adult respiratory distress syndrome, osteoporosis, restenosis, reperfusion injury, diabetes, transplant rejection, inflammatory bowel disease, ulcerative colitis, etc. Other specifically claimed compounds include the following:



Compound	R1	Formula
292369	OMe	C ₁₈ H ₁₂ FN ₃ O
292370	OPh	C ₂₁ H ₁₄ FN ₃ O
292371	NH2	C ₁₅ H ₁₁ FN ₄
292372	2-Me-PhNH	C ₂₂ H ₁₇ FN ₄

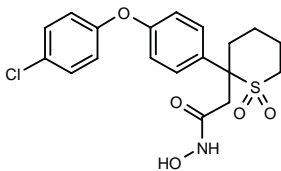
SOURCE – SmithKline Beecham.

REFERENCES

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292415

2-[2-[4-(4-Chlorophenoxy)phenyl]-1,1-dioxohexahydro-thiopyran-2-yl]acetohydroxamic acid



C19 H20 Cl N O5 S; Mol wt: 409.8880

ACTION – Inhibitor of matrix metalloproteinases (MMPs) and TNF- α , particularly active against collagenases (MMP-1, MMP-8 and MMP-13), with an IC₅₀ value of 2.2 nM for inhibition of human MMP-13. It is expected to be useful for the treatment of rheumatoid arthritis, periodontal disease, corneal ulceration, tumor metastasis, osteoarthritis, restenosis following angioplasty, osteoporosis, psoriasis, chronic active hepatitis, autoimmune keratitis and the like.

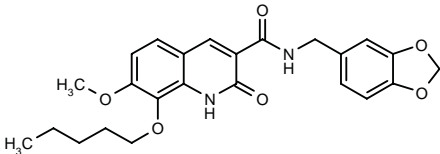
SOURCE – Fujisawa.

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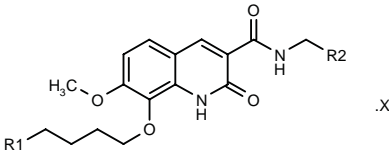
292443

N-(1,3-Benzodioxol-5-ylmethyl)-7-methoxy-2-oxo-8-(pentyloxy)-1,2-dihydroquinoline-3-carboxamide



C24 H26 N2 O6; Mol wt: 438.4774

ACTION – Agent with very high affinity and selectivity for peripheral cannabinoid CB₂ receptors, as demonstrated in binding assays using human CB₁ and CB₂ receptors (K_i = 3436 and 0.087 nM, respectively). This compound also showed excellent oral activity in the carrageenan-induced rat paw edema model with an ED₅₀ < 0.10 mg/kg. Potentially useful as an immunosuppressant, antiinflammatory and antiallergic agent. Other compounds within this series of 2-oxoquinoline derivatives are:



Compound	R1	R2	X	Formula
292444	Me	4-Pyr		C ₂₂ H ₂₆ N ₂ O ₄
292445	Me	4-morpholinyl-CH2		C ₂₂ H ₃₁ N ₃ O ₅
292446	H	4-F-PhCH2		C ₂₃ H ₂₅ FN ₂ O ₄
292447	H	4-Pyr-CH2	HCl	C ₂₂ H ₂₆ N ₃ O ₄ ·HCl
292448	Me	4-Cl-PhCH2		C ₂₄ H ₂₇ ClN ₂ O ₄

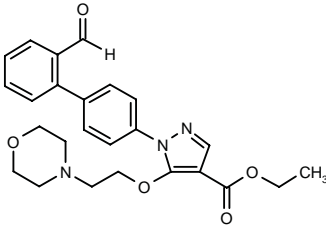
SOURCE – Japan Tobacco.

REFERENCES

1. Inaba, T. et al. (Japan Tobacco Inc.) *2-Oxoquinoline cpds. and medicinal uses thereof.* JP 2000256323, WO 0040562.

292989

1-(2'-Formylbiphenyl-4-yl)-5-[2-(4-morpholinyl)ethoxy]-1H-pyrazole-4-carboxylic acid ethyl ester



C25 H27 N3 O5; Mol wt: 449.5043

ACTION – Peripheral cannabinoid CB₂ receptor modulator, potentially useful for the treatment of immunologically mediated inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, multiple sclerosis, diabetes and thyroiditis, as well as for the therapy of ankylosing spondylitis, gout, gouty arthritis, osteoarthritis, osteoporosis and renal ischemia.

SOURCE – SmithKline Beecham.

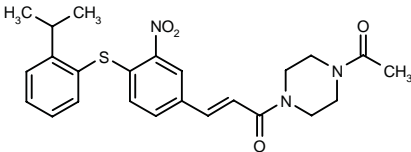
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1. Xiang, J.-N. et al. (SmithKline Beecham Corp.) *Cannabinoid receptor modulators.* US 6100259, WO 9831227.

A-286982

292239

1-(4-Acetyl piperazin-1-yl)-3-[4-(2-isopropylphenyl)sulfanyl]-3-nitrophenyl]-2(E)-propen-1-one



C24 H27 N3 O4 S; Mol wt: 453.5603

ACTION – Nonpeptide inhibitor of the interaction between LFA-1 (CD18/CD11a) and ICAM-1 (IC₅₀ = 44 and 35 nM in LFA-1/ICAM-1 biochemical assay and LFA-1/ICAM-1-mediated cellular adhesion assay, respectively), potentially useful for the treatment of inflammatory and immune diseases.

SOURCE – Abbott.

REFERENCES

1. Link, J. et al. (Abbott Laboratories Inc.) *Cell adhesion-inhibiting antiinflammatory and immune-suppressive cpds.* US 6110922, WO 0039081.

2. Link, J. et al. (Abbott Laboratories Inc.) *Cell adhesion-inhibiting antiinflammatory and immune-suppressive cpds.* WO 0059880.

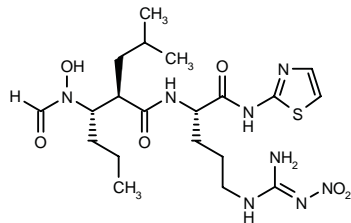
3. Liu, G. et al. *Discovery of novel p-arylthio cinnamides as antagonists of LFA-1/ICAM-1 interaction. I. Identification of an additional binding site based on an anilino diaryl sulfide lead.* 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 171.

4. Liu, G. et al. *Discovery of novel p-arylthio cinnamides as antagonists of leukocyte function-associated antigen-1/intracellular adhesion molecule-1 interaction. 1. Identification of an additional binding pocket based on an anilido diaryl sulfide lead.* J Med Chem 2000, 43(21): 4025.

GW-4459*

287172

N^α-[3(*S*)-(N-Formyl-N-hydroxyamino)-2(*R*)-isobutyl-hexanoyl]-*N*^ω-nitro-*N*¹-(2-thiazolyl)-L-argininamide



C20 H34 N8 O6 S; Mol wt: 514.6046

ACTION – Potent, water-soluble inhibitor of TNF- α -converting enzyme (TACE; IC₅₀ = 4 nM) proven to inhibit TNF release from whole cells *in vitro* (IC₅₀ = 31 nM). In a rat zymosan-induced pleurisy model, compound significantly inhibited TNF accumulation in the pleural fluid (33%) when given at a dose of 10 mg/ml s.c. prior to zymosan injection.

SOURCE – Glaxo Wellcome.

REFERENCES

1. Andrews, R.C. et al. (Glaxo Group Ltd.) *Formamide cpds. as therapeutic agents*. WO 0012466.

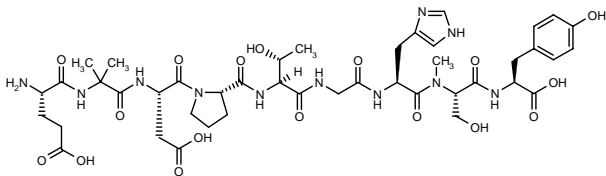
2. Rabinowitz, M. et al. *Synthesis and evaluation of novel N-hydroxy formamide inhibitors of tumor necrosis factor alpha converting enzyme*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 173.

*Identified compound **287172** Drug Data Rep 2000, 022(06): 0545.

IMMUNOMODULATING AGENTS

291717

L-Glutamyl-2-aminoisobutyryl-L-aspartyl-L-prolyl-L-threonyl-glycyl-L-histidyl-(N-methyl)-L-seryl-L-tyrosine



C43 H61 N11 O17; Mol wt: 1004.0150

ACTION – Structurally modified analogue of the tumor antigen MZ2-E that binds to an HLA molecule on the cell surface to form a complex that may be recognized by cytolytic T-lymphocytes, producing lysis of the cell. It was able to sensitize target BM21 cells to lysis at a concentration comparable to that of the parent MZ2-E antigen, and it was completely resistant to peptidase degradation. This peptide is useful as an immunogen and in diagnostic assays.

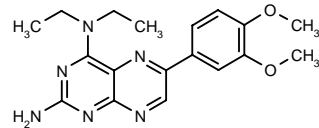
SOURCE – Ludwig Institute for Cancer Research, New York, NY (US).

REFERENCES

1. Gairin, J.E. et al. (Ludwig Institute for Cancer Research) *Structurally modified peptides that are resistant to peptidase degradation*. US 6087441.

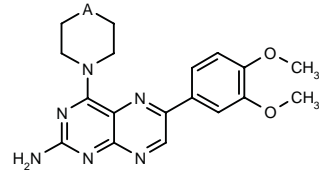
292236

6-(3,4-Dimethoxyphenyl)-*N*⁴,*N*⁴-diethylpteridine-2,4-diamine



C18 H22 N6 O2; Mol wt: 354.4118

ACTION – Immunosuppressive agent with potential utility in the treatment of autoimmune disorders, the prevention of transplant rejection and the treatment of inflammatory diseases. Other exemplified pteridine derivatives are:



Compound	A	Formula
292237	O	C ₁₈ H ₂₀ N ₆ O ₃
292238	CH2	C ₁₉ H ₂₂ N ₆ O ₂

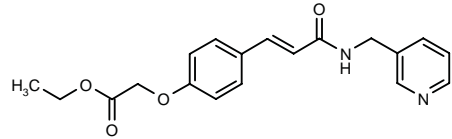
SOURCE – Katholieke Universiteit Leuven, Leuven (BE).

REFERENCES

1. Waer, M.J.A. et al. (K.U. Leuven Research & Development) *Immunosuppressive effects of pteridine derivs*. WO 0039129.

292578

2-[4-[3-Oxo-3-(3-pyridinylmethylamino)-1(*E*)-propenyl]-phenoxy]acetic acid ethyl ester



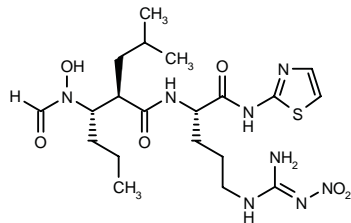
C19 H20 N2 O4; Mol wt: 340.3770

ACTION – Immunomodulating agent also reported to be useful for the treatment or prevention of nephrotic syndrome, circulatory disorders and respiratory diseases, a representative compound from a series of cinnamamide derivatives. Compound inhibited the production of IL-6, IL-10 and IL-12 by 40.4, 23.7 and 64.6%, respectively, at 10 μ g/ml in murine peritoneal macrophages. In addition, it was effective in a nephrotic model in rats, reducing protein excretion in urine, and was shown to inhibit collagen- and arachidonic acid-induced TxB₂ production by 32 and 67%, respectively, at 10 μ M in rat platelet-rich plasma (PRP). Other exemplified compounds include the following:

GW-4459*

287172

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SOURCE – Glaxo Wellcome.

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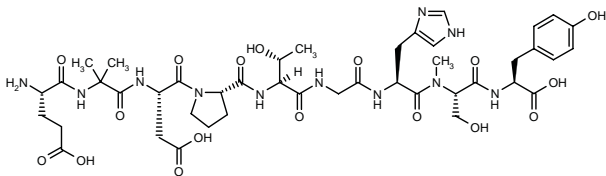
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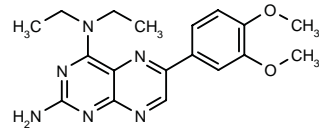
SOURCE – Ludwig Institute for Cancer Research, New York, NY (US).

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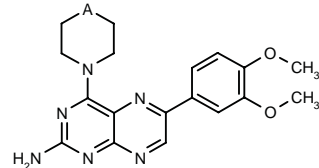
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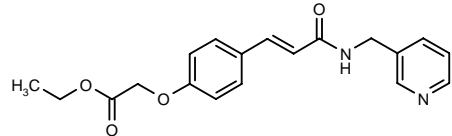
SOURCE – Katholieke Universiteit Leuven, Leuven (BE).

REFERENCES

1. Waer, M.J.A. et al. (K.U. Leuven Research & Development) *Immunosuppressive effects of pteridine derivs*. WO 0039129.

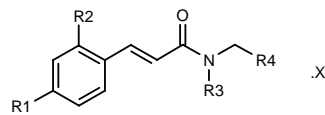
292578

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Compound	R1	R2	R3	R4	X	Formula
292579	OCH2CO2Et	H	H	3-Pyr-CH2		C ₂₀ H ₂₂ N ₂ O ₄
292580	H	OCH2-CONHOH	H	3-Pyr		C ₁₇ H ₁₇ N ₃ O ₄
292581	OCH2CO2H	H	Me	3-Pyr	HCl	C ₁₈ H ₁₈ N ₂ O ₄ .HCl

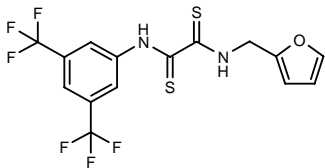
SOURCE – Tsumura.

REFERENCES

1. Hasegawa, Y. et al. (Tsumura & Co.) *Cinnamide derivs. and drug compsns. containing the same*. WO 0042013.

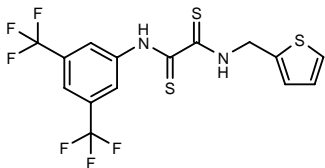
292599

N-[3,5-Bis(trifluoromethyl)phenyl]-N'-(2-furylmethyl)-dithioamide



C15 H10 F6 N2 O S2; Mol wt: 412.3770

ACTION – Immunostimulating, antiviral and antitumor agent shown to concentration-dependently (1-25 μM) potentiate concanavalin A (ConA)-stimulated murine spleen cell proliferation, being more potent than tucaresol, and to stimulate murine spleen cell proliferation in a mixed lymphocyte reaction (MLR) at 1 and 10 μM. In addition, compound increased IL-2 production in ConA-stimulated human peripheral blood monocytes and in anti-CD3 monoclonal antibody-stimulated Jurkat cells. Antiviral activity was seen against murine cytomegalovirus (MCMV) infection in mice at 10 and 50 mg/kg i.p. and it inhibited Lewis lung cancer metastasis in mice at 0.3-30 mg/kg p.o. Another exemplified compound from this series of amide and thioamide derivatives is:



292600: C15 H10 F6 N2 S3

SOURCE – Japan Tobacco.

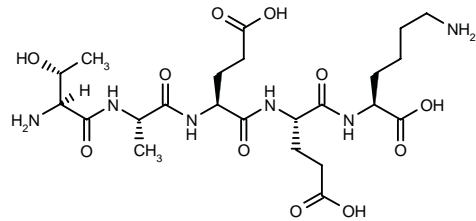
REFERENCES

1. Hagiwara, A. et al. (Japan Tobacco Inc.) *Cpds. having immunopotentiative activity*. JP 2000178248.

HM-897

292903

L-Threonyl-L-alanyl-L-glutamyl-L-glutamyl-L-lysine



C23 H40 N6 O11; Mol wt: 576.6000

ACTION – Immunomodulating peptide for the treatment or prevention of infections in immunodepressed states, and for the treatment of immunodeficient states, particularly AIDS. This peptide is particularly useful for enhancing the immune response to vaccines and is also reported to be of use for the treatment of atopic states, anemias and immune disorders. Results from studies in guinea pigs suggested that HM-897 stimulates the proliferation of lymphocytes in the lymphoid organs without directly activating neutrophils in peripheral blood. In 5-FU-immunosuppressed mice, HM-897 induced an increase in the total number of leukocytes and neutrophils, an insignificant decrease in the number of monocytes and a decrease to normal range in peripheral blood lymphocytes. Although HM-897 alone appeared to have no specific antimicrobial activity *in vitro*, it was found to promote survival of animals injected with a lethal dose of *Staphylococcus aureus*, demonstrating a synergistic effect when combined with an antibiotic such as ampicillin.

SOURCE – Cytran.

REFERENCES

1. Green, L.R. et al. (Cytran, Inc.) *Immunomodulating peptides and methods of use*. US 6100380.

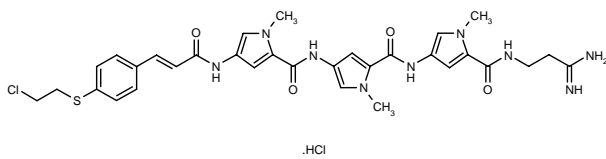
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

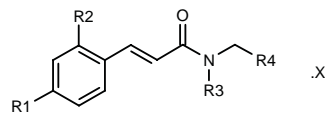
PNU-193821

291930

N-[5-[N-(2-Amidinoethyl)carbamoyl]-1-methyl-1H-pyrrol-3-yl]-4-[4-[3-[4-(2-chloroethylsulfanyl)phenyl]-2(E)-propenamido]-1-methyl-1H-pyrrol-2-ylcarboxamido]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride



C32 H36 Cl N9 O4 S . HCl; Mol wt: 714.6753



Compound	R1	R2	R3	R4	X	Formula
292579	OCH2CO2Et	H	H	3-Pyr-CH2		C ₂₀ H ₂₂ N ₂ O ₄
292580	H	OCH2-CONHOH	H	3-Pyr		C ₁₇ H ₁₇ N ₃ O ₄
292581	OCH2CO2H	H	Me	3-Pyr	HCl	C ₁₈ H ₁₈ N ₂ O ₄ .HCl

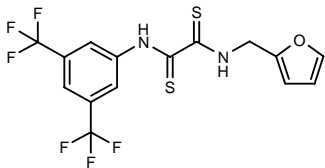
SOURCE – Tsumura.

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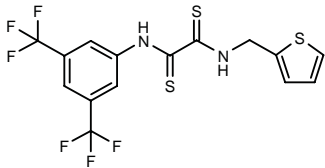
292599

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C15 H10 F6 N2 O S2; Mol wt: 412.3770

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292600: C15 H10 F6 N2 S3

SOURCE – Japan Tobacco.

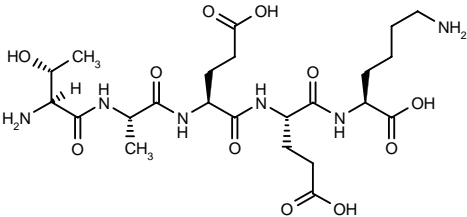
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HM-897

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L-Threonyl-L-alanyl-L-glutamyl-L-glutamyl-L-lysine



C23 H40 N6 O11; Mol wt: 576.6000

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SOURCE – Cytran.

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1. Green, L.R. et al. (Cytran, Inc.) *Immunomodulating peptides and methods of use*. US 6100380.

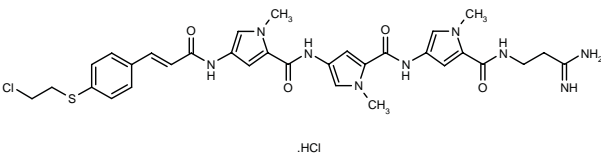
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

PNU-193821

291930

N-[5-[N-(2-Amidinoethyl)carbamoyl]-1-methyl-1H-pyrrol-3-yl]-4-[4-[3-[4-(2-chloroethylsulfanyl)phenyl]-2(E)-propenamido]-1-methyl-1H-pyrrol-2-ylcarboxamido]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride



C32 H36 Cl N9 O4 S . HCl; Mol wt: 714.6753

ACTION – Antineoplastic agent, a phenyl sulfur mustard derivative of distamycin A with strong cytotoxic activity against leukemia L1210 cells ($IC_{50} = 0.9 \text{ nM}$). Compound was about 1,000-fold more cytotoxic against L1210 cells than the classical nitrogen mustard melphalan.

SOURCE – Pharmacia.

REFERENCES

1. Cozzi, P. et al. (Pharmacia & Upjohn SpA) *Sulfurated distamycin derivs., process for preparing them, and their use as antitumor agents*. WO 0006541.

2. Beria, I. et al. *Phenyl sulfur mustard derivatives of distamycin A*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PC-29.

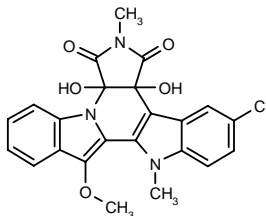
3. Cozzi, P. et al. *Phenyl sulfur mustard derivatives of distamycin A*. Bioorg Med Chem Lett 2000, 10(15): 1653.

ANTIBIOTICS AND ALKALOIDS

BE-54017

292618

10-Chloro-5a,8a-dihydroxy-14-methoxy-7,13-dimethyl-5a,6,7,8,8a,13-hexahydropyrrolo[3',4':5,6]pyrido-[1,2-a:3,4-b']diindole-6,8-dione



C23 H18 Cl N3 O5; Mol wt: 451.8642

ACTION – Antitumor substance isolated from *Streptomyces* sp. A54017 (FERM P-16952). BE-54017 was found to be active against murine leukemia P388, human colon cancer DLD-1 and human lung cancer PC-13 cells, with respective IC_{50} values of 0.11, 0.15 and 0.69 $\mu\text{g/ml}$.

SOURCE – Banyu.

REFERENCES

1. Nakase, K. et al. (Banyu Pharmaceutical Co., Ltd.) *Anti-tumor substance BE-54017 and its preparation method*. JP 2000178274.

DNA-INTERCALATING DRUGS

291739

L-Threonyl-L-glutaminy-L-leucyl-L-aspartyl-L-isoleucyl-L-leucyl-L-arginyl-L-aspartyl-L-leucyl-L-phenylalanyl-L-glutamyl-L-leucyl-L-arginyl-L-leucyl-L-lysyl-L-tyrosyl-L-tyrosyl-glycyl-L-leucyl-L-arginyl-L-lysyl-L-glutamyl-L-phenylalanyl-L-leucyl-L-leucyl-L-glutaminy-L-methionyl-L-leucyl-glycine

C167 H270 N42 O43 S; Mol wt: 3586.2870

ACTION – Antitumor agent, a potent inhibitor of DNA topoisomerase II demonstrating complete inhibition of human α -topoisomerase II at a concentration of 0.5 μM in *in vitro* assays.

SOURCE – Lafon.

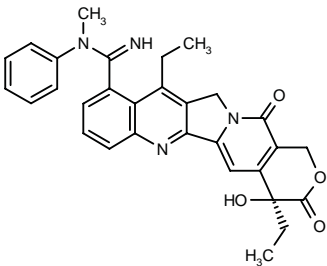
REFERENCES

1. Fermandjian, S. et al. (Laboratoires L. Lafon) *Topoisomerase II inhibitor*. FR 2787454, WO 0037499.

PNU-166300

292076

4(S),11-Diethyl-4-hydroxy-N-methyl-3,14-dioxo-N-phenyl-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]-quinoline-10-carboxamide



C30 H28 N4 O4; Mol wt: 508.5752

ACTION – Water-soluble camptothecin derivative proven to exert potent antitumor activity comparable to that of topotecan and a higher therapeutic index (LD_{10}/ED_{50}), exhibiting T/C values of 200% at 15 mg/kg i.v. and 212% at 22.5 mg/kg i.v. in mice bearing L1210 leukemia and a therapeutic index of 4; topotecan in the same test displayed a T/C of 172% at 15 mg/kg i.v. and a therapeutic index of 1.3.

SOURCE – Pharmacia.

REFERENCES

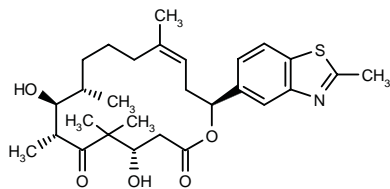
1. Bedeschi, A. et al. (Pharmacia & Upjohn SpA) *Amidino-camptothecin derivs*. US 6093721, WO 9905103.

ANTIMITOTIC DRUGS

291845

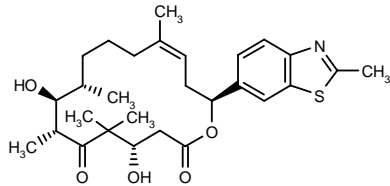
(4*S*,7*R*,8*S*,9*S*,16*S*)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methylbenzothiazol-5-yl)-1-oxa-13-cyclohexadecene-2,6-dione

(3*S*,6*R*,7*S*,8*S*,15*S*)-3,7-Dihydroxy-4,4,6,8,12-pentamethyl-15-(2-methylbenzothiazol-5-yl)-12-pentadeceno-15-lactone

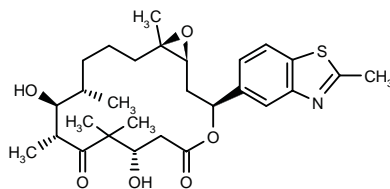


C28 H39 N O5 S; Mol wt: 501.6841

ACTION – Epothilone derivative that inhibits microtubule depolymerization and is potentially useful for the treatment of proliferatives diseases, especially for the therapy of tumors including metastasis. Other specifically claimed compounds are:



291846: C28 H39 N O5 S



291847: C28 H39 N O6 S

SOURCE – Novartis.

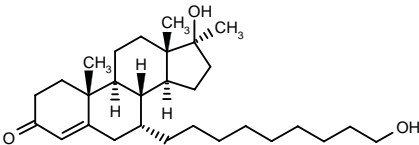
REFERENCES

1. Altmann, K.-H. et al. (Novartis AG) *Epothilone derivs. and their use as antitumor agents*. WO 0037473.

HORMONAL AGENTS

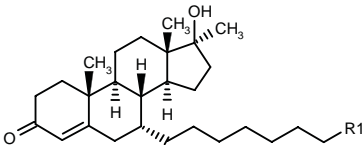
292311

17β-Hydroxy-7α-(9-hydroxynonyl)-17α-methylandro-4-en-3-one



C29 H48 O3; Mol wt: 444.6952

ACTION – Antiandrogenic agent (IC₅₀ = 40 nM) for the long-term therapy of androgen-dependent diseases such as prostate carcinoma. Other compounds from this series of 7α,17α-bis-alkylated testosterone derivatives are:



Compound	R1	Formula
292312	SAC	C ₂₉ H ₄₆ O ₃ S
292313	O(CH ₂) ₄ CN	C ₃₂ H ₅₁ NO ₃

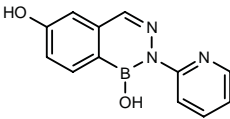
SOURCE – Schering AG.

REFERENCES

1. Cleve, A. et al. (Schering AG) *New 7-α,17-α-bis-alkylated testosterone derivs. and their use in long-term therapy of androgen-dependent diseases*. DE 19860719, WO 0039148.

292913

2-(2-Pyridyl)-1,2-dihydro-2,3,1-benzodiazaborine-1,6-diol



C12 H10 B N3 O2; Mol wt: 239.0410

ACTION – Boron heterocycle steroid mimic proven to induce concentration-dependent inhibition of cell growth in culture using human breast cancer MCF-7 cells. Potentially useful for the treatment of estrogen-dependent cancers, as well as in nuclear magnetic resonance imaging and boron neutron capture therapy.

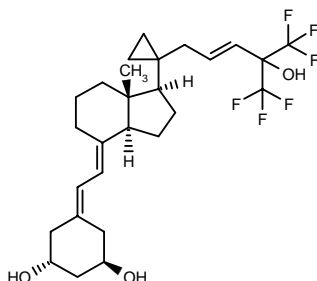
SOURCE – SRI.

REFERENCES

1. Groziak, M.P. (SRI International) *Boron steroid mimics and pharmaceutical compsns*. WO 0043401.

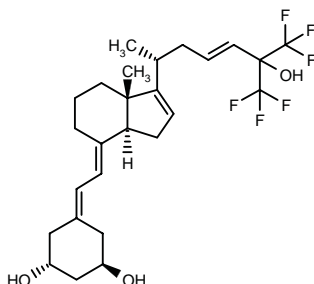
RO-27-0574^{2,4,6}**292496**

26,26,26,27,27,27-Hexafluoro-1 α ,25-dihydroxy-20,21-methylene-23,24-didehydro-19-norvitamin D₃



C27 H36 F6 O3; Mol wt: 522.5664

ACTION – Antineoplastic agent, a vitamin D₃ analogue proven to strongly inhibit clonal proliferation of promyelocytic leukemia HL-60 cells and breast cancer MCF-7 cells (IC₅₀ = 0.2 and 0.4 nM, respectively), as well as prostate cancer LNCaP and PC-3 cells (IC₅₀ = 0.3 and 0.9 nM, respectively). Compound induced cell cycle arrest in the G0/G1 phase, with a concomitant decrease of cells in the S phase, and it increased levels of the cyclin-dependent kinase inhibitors p21^{Waf1} and p27^{Kip1}. *In vivo*, doses of 0.005 and 0.01 μ g for 6 weeks induced significant growth delay in prostate PC-3 tumors grafted onto nude mice. It was more active than vitamin D₃ but did not induce hypercalcemia. Another related 1,25(OH)₂D₃ analogue is:



Ro-25-9022 [292497]^{1,3,5,6}: C26 H34 F6 O3

SOURCE – Roche.

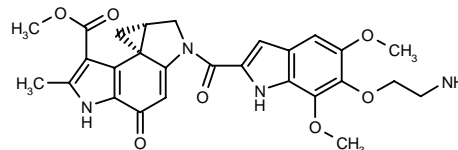
REFERENCES

1. Doran, T.I. et al. (F. Hoffmann-La Roche AG) *Vitamin D₃ analogs*. EP 0654467, JP 1995188159, US 5428029.
2. Manchand, P.S. and Uskokovic, M.R. (F. Hoffmann-La Roche AG) *1,3-Dihydroxy-20,20-dialkyl-vitamin D₃ analogs*. EP 1015423, WO 9912894.
3. Evans, S.R.T. et al. *1,25-Dihydroxyvitamin D₃ synthetic analogs inhibit spontaneous metastases in a 1,2-dimethylhydrazine-induced colon carcinogenesis model*. Int J Oncol 2000, 16(6): 1249.
4. Koike, M. et al. *20-Cyclopropyl-cholecalciferol vitamin D₃ analogs: A unique class of potent inhibitors of proliferation of human prostate, breast and myeloid leukemia cell lines*. Anticancer Res 1999, 19(3A): 1689.
5. Kubota, T. et al. *19-Nor-26,27-bishomo-vitamin D₃ analogs: A unique class of potent inhibitors of proliferation of prostate, breast, and hematopoietic cancer cells*. Cancer Res 1998, 58(15): 3370.
6. Uskokovic, M.R. et al. *Synthesis and antitumor activity of 1,25(OH)₂-23-ene-26,27F6-19-nor-20-cyclopropyl D₃, Ro 27-0574*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 194.

CANCER IMMUNOTHERAPY**293270**

Immunoconjugate consisting of the duocarmycin derivative DU-257 covalently linked to the KM231 monoclonal antibody via a poly(ethylene glycol)dipeptidyl linker

ACTION – Immunoconjugate consisting of the duocarmycin derivative **DU-257** linked to the murine monoclonal antibody KM231 that reacts with sialyl Lewis a (sLe^a), a carbohydrate antigen overexpressed on the surface of a number of tumor cells, via a PEG-dipeptidyl linker. The conjugate exhibited significant growth-inhibitory activity in human colorectal carcinoma SW116 cells (which express the sLe^a antigen), while no effect was seen in antigen-negative HeLa S3 cells. Potentially useful for the treatment of sLe^a-positive tumors.



DU-257 [292880]: C27 H28 N4 O7

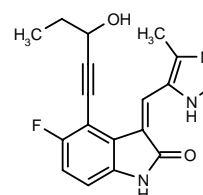
SOURCE – Kyowa Hakko.

REFERENCES

1. Suzawa, T. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Toxin conjugates*. US 6103236, WO 9635451.
2. Suzawa, T. et al. *Synthesis of a novel duocarmycin derivative DU-257 and its application to immunoconjugate using poly(ethylene glycol)-dipeptidyl linker capable of tumor specific activation*. Bioorg Med Chem 2000, 8(8): 2175.

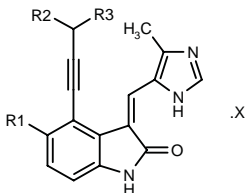
INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS**291732**

(*Z*)-5-Fluoro-4-(3-hydroxy-1-pentynyl)-3-(4-methyl-1*H*-imidazol-5-ylmethylene)-2,3-dihydro-1*H*-indol-2-one



C18 H16 F N3 O2; Mol wt: 325.3414

ACTION – Cyclin-dependent kinase inhibitor, particularly active against CDK2, for the treatment of proliferative disorders, especially solid tumors such as breast and colon tumors. The compound was found to inhibit phosphorylation of purified recombinant retinoblastoma protein ($IC_{50} < 4.0\text{ }\mu\text{M}$) and demonstrated antiproliferative activity in cell-based assays using estrogen receptor-negative epithelial breast carcinoma MDA-MB-435 ($IC_{50} < 3.5\text{ }\mu\text{M}$) and colon carcinoma SW480 ($IC_{50} < 1.0\text{ }\mu\text{M}$) cell lines. Other exemplified compounds from this series of 4-alkenyl(or alkynyl)oxindoles are:



Compound	R1	R2	R3	X	Formula
291733	NO2	OH	Et		C ₁₈ H ₁₆ N ₄ O ₄
291734	F	H	NHMe	CF ₃ CO ₂ H	C ₁₇ H ₁₅ FN ₄ O.C ₂ HF ₃ O ₂

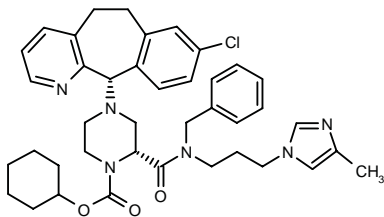
SOURCE – Roche.

REFERENCES

1. Chen, Y. et al. (F. Hoffmann-La Roche AG) 4-Alkenyl (and alkynyl) oxindoles as inhibitors of cyclin-dependent kinases, in particular CDK2. US 6130239, WO 0035908.

291869

4-[8-Chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*S*)-yl]-2(*R*)-[*N*-benzyl-*N*-[3-(4-methyl-1*H*-imidazol-1-yl)propyl]carbamoyl]piperazine-1-carboxylic acid cyclohexyl ester



C40 H47 Cl N6 O3; Mol wt: 695.3033

ACTION – Protein farnesyltransferase inhibitor ($IC_{50} = 0.036\text{ nM}$) shown to inhibit the anchorage-dependent growth of human tumor cell lines in the soft agar assay ($IC_{50} = 2\text{ nM}$). Potentially useful for the treatment of tumors expressing an activated Ras oncogene including, but not limited to, lung, pancreatic, colon, breast and prostate cancers, myeloid leukemias, thyroid follicular cancer, myelodysplastic syndrome, bladder carcinoma, epithelial carcinoma and melanoma.

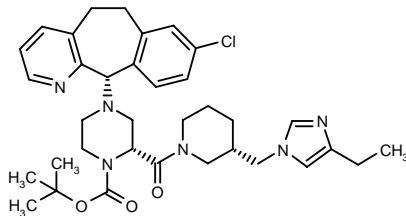
SOURCE – Schering-Plough.

REFERENCES

1. Taveras, A.G. et al. (Schering Corp.) Tricyclic farnesyl protein transferase inhibitors. WO 0037459.

291870

4-[8-Chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*S*)-yl]-2(*R*)-[3(*R*)-(4-ethyl-1*H*-imidazol-1-ylmethyl)piperidin-1-ylcarbonyl]piperazine-1-carboxylic acid *tert*-butyl ester



C35 H45 Cl N6 O3; Mol wt: 633.2325

ACTION – Protein farnesyltransferase inhibitor exhibiting an IC_{50} value in the range $< 0.04\text{ nM}$ to 6.7 nM when tested *in vitro* for inhibition of protein farnesyltransferase; it also inhibited the anchorage-dependent growth of human tumor cell lines in the soft agar assay with IC_{50} values in the range of $< 0.05\text{ nM}$ to 30 nM . Potentially useful for the treatment of tumors expressing an activated Ras oncogene including, but not limited to, lung, pancreatic, colon, breast and prostate cancers, myeloid leukemias, thyroid follicular cancer, myelodysplastic syndrome, bladder carcinoma, epithelial carcinoma and melanoma.

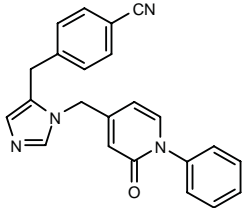
SOURCE – Schering-Plough.

REFERENCES

1. Guzi, T. et al. (Schering Corp.) Farnesyl protein transferase inhibitors. WO 0037458.

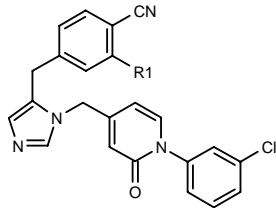
292077

4-[1-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-1*H*-imidazol-5-ylmethyl]benzonitrile



C23 H18 N4 O; Mol wt: 366.4222

ACTION – Inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras, displaying an $IC_{50} < 50\text{ }\mu\text{M}$ against human enzyme. Potentially useful as an antineoplastic agent. Other specifically claimed compounds are:



Compound	R1	Formula
292078	H	C ₂₃ H ₁₇ ClN ₄ O
292079	OMe	C ₂₄ H ₁₉ ClN ₄ O ₂

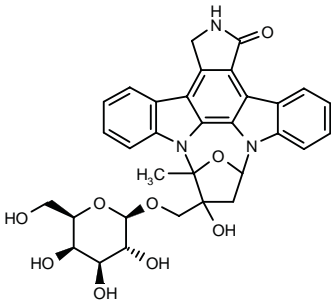
SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. et al. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. US 6093737.

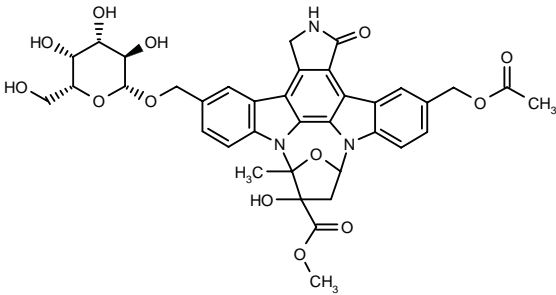
292188

9,12-Epoxy-10-(β-D-galactopyranosyloxymethyl)-10-hydroxy-9-methyl-2,3,9,10,11,12-hexahydro-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*k*]pyrrolo[3,4-*l*]benzodiazocin-1-one



C32 H31 N3 O9; Mol wt: 601.6089

ACTION – Protein kinase C (PKC) inhibitor (IC₅₀ = 0.057 nM), potentially useful for the treatment of PKC-mediated diseases such as neoplastic diseases, psoriasis and eczema. Another glycosidic indolocarbazole derivative is:



292189: C37 H37 N3 O13

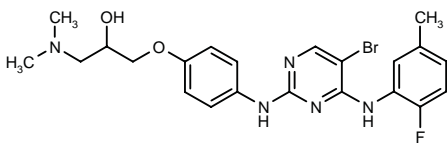
SOURCE – Kyowa Hakko.

REFERENCES

1. Mochida, K. and Ue, H. (Kyowa Hakko Kogyo Co., Ltd.) *Glycosidic indolocarbazole derivs. and their preparation method*. JP 2000169496.

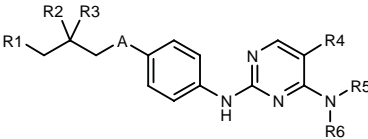
292225

1-[4-[5-Bromo-4-(2-fluoro-5-methylphenylamino)-pyrimidin-2-ylamino]phenoxy]-3-(dimethylamino)propan-2-ol



C22 H25 Br F N5 O2; Mol wt: 490.3745

ACTION – Inhibitor of cell cycle kinases with selectivity for cyclin-dependent kinases CDK2, CDK4 and CDK6, and which also inhibits focal adhesion kinase (FAK). In *in vitro* assays, the compound inhibited CDK4 activity with an IC₅₀ of 0.02 μM. These properties make it potentially useful in the treatment of cancers, especially solid tumors and leukemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, hemangioma, atherosclerosis, restenosis, autoimmune diseases and ocular diseases associated with retinal vessel proliferation. Other exemplified pyrimidine compounds are:



Compound	R1	R2	R3	R4	R5	R6	A	Formula
292226	N(Me)2	OH	H	Br	H	Ph	O	C ₂₁ H ₂₄ BrN ₅ O ₂
292227	N(Me)2	OH	H	NO2	H	2-F-Ph	O	C ₂₁ H ₂₃ FN ₅ O ₄
292228	i-PrNH	H	H	Br	H	2-Pyr	NH	C ₂₁ H ₂₆ BrN ₇
292229	N(Me)2	OH	H	Br	H	2-Pyr	O	C ₂₀ H ₂₃ BrN ₆ O ₂
292230	i-PrNH	OH	H	Br	H	6-Me-2-Pyr	O	C ₂₂ H ₂₇ BrN ₆ O ₂
292231	i-PrNH	OH	H	Br	H	Ph	O	C ₂₂ H ₂₆ BrN ₅ O ₂
292232	1-imidazolyl	H	H	Br	H	6-Me-2-Pyr	O	C ₂₂ H ₂₂ BrN ₇ O
292233	i-PrNH	OH	Me	Br	H	Ph	O	C ₂₃ H ₂₈ BrN ₅ O ₂
292234	N(Me)2	OH	H	Br	H	4-Cl-Ph	O	C ₂₁ H ₂₃ BrClN ₅ O ₂
292235	N(Me)2	OH	H	Br	(CH2)3-CF3	Ph	O	C ₂₅ H ₂₉ BrF ₃ N ₅ O ₂

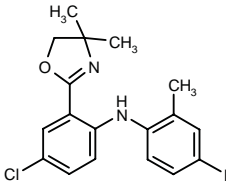
SOURCE – AstraZeneca.

REFERENCES

1. Bradbury, R.H. et al. (AstraZeneca UK, Ltd.) *Pyrimidine cpds*. WO 0039101.

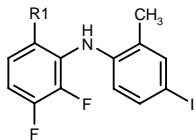
292554

N-[4-Chloro-2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]-*N*-(4-iodo-2-methylphenyl)amine



C18 H18 Cl I N2 O; Mol wt: 440.7062

ACTION – Selective inhibitor of MEK kinase, potentially useful for the treatment of proliferative diseases, cancer, stroke, heart failure, xenograft rejection, arthritis, cystic fibrosis, hepatomegaly, cardiomegaly, Alzheimer's disease, diabetic complications, septic shock and viral infections. Other exemplified 1-heterocycle substituted diarylamines are:



Compound	R1	Formula
292555	5-tetrazolyl	C ₁₄ H ₁₀ F ₂ IN ₅
292556	4,4-(Me)2-4,5-dihydro-2-oxazolyl	C ₁₈ H ₁₇ F ₂ IN ₂ O
292557	CO ₂ Me	C ₁₅ H ₁₂ F ₂ INO ₂
292558	3-NH2-1,2,4-triazol-5-yl	C ₁₅ H ₁₂ F ₂ IN ₅
292559	3-NH2-1,2,4-oxadiazol-5-yl	C ₁₅ H ₁₁ F ₂ IN ₄ O
292560	CONHNHCSNH2	C ₁₅ H ₁₃ F ₂ IN ₄ OS
292561	5-thioxo-4,5-dihydro-1,2,4-triazol-3-yl	C ₁₅ H ₁₁ F ₂ IN ₄ S
292562	1,3,4-oxadiazol-2-yl	C ₁₅ H ₁₀ F ₂ IN ₃ O
292564	5-SH-1,3,4-oxadiazol-2-yl	C ₁₅ H ₁₀ F ₂ IN ₃ OS

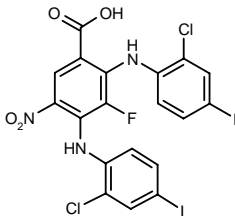
SOURCE – Pfizer.

REFERENCES

1. Tecle, H. et al. (Pfizer Inc.) *1-Heterocycle subst. diarylamines*. JP 2000204077, WO 0042029.

292567

2,4-Bis(2-chloro-4-iodophenylamino)-3-fluoro-5-nitro-benzoic acid



C19 H10 Cl2 F I2 N3 O4; Mol wt: 688.0090

ACTION – Selective inhibitor of MEK kinase, a representative compound from a series of diarylamines that are potentially useful for the treatment of proliferative diseases, cancer, stroke, heart failure, xenograft rejection, arthritis, cystic fibrosis, hepatomegaly, cardiomegaly, Alzheimer’s disease, diabetic complications, septic shock and viral infections.

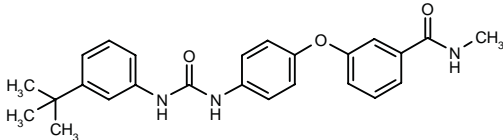
SOURCE – Pfizer.

REFERENCES

1. Barrett, S.D. and Tecle, H. (Pfizer Inc.) *4-Arylamino, 4-aryloxy, and 4-arylthio diarylamines and derivs. thereof as selective MEK inhibitors*. JP 2000204068, WO 0041994.

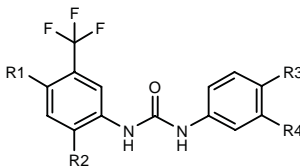
292660

3-[4-[N’-(3-*tert*-Butylphenyl)ureido]phenoxy]-*N*-methyl-benzamide

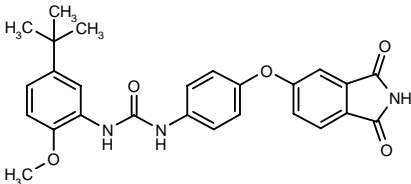


C25 H27 N3 O3; Mol wt: 417.5063

ACTION – Raf kinase inhibitor for the treatment of tumors and cancer cell growth mediated by the Ras protein signal transduction cascade, for example solid tumors. Other specifically claimed aryl ureas include the following:



Compound	R1	R2	R3	R4	Formula
292662	H	OMe	H	2-(NH ₂ CO)-4-Pyr-O	C ₂₁ H ₁₇ F ₃ N ₄ O ₄
292663	H	OMe	2-(MeNHCO)-4-Pyr-S	H	C ₂₂ H ₁₉ F ₃ N ₄ O ₃ S
292665	Cl	H	H	2-(NH ₂ CO)-4-Pyr-O	C ₂₀ H ₁₄ ClF ₃ N ₄ O ₃
292666	Br	H	H	2-(MeNHCO)-4-Pyr-O	C ₂₁ H ₁₆ BrF ₃ N ₄ O ₃
292667	Br	H	2-(MeNHCO)-4-Pyr-O	Cl	C ₂₁ H ₁₅ BrClF ₃ N ₄ O ₃
292668	Cl	OMe	H	2-(MeNHCO)-4-Pyr-O	C ₂₂ H ₁₈ ClF ₃ N ₄ O ₄
292671	Cl	OMe	2-(MeNHCO)-4-Pyr-O	Cl	C ₂₂ H ₁₇ Cl ₂ F ₃ N ₄ O ₄



292661: C26 H25 N3 O5

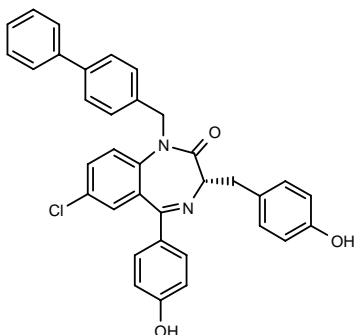
SOURCE – Bayer.

REFERENCES

1. Riedl, B. et al. (Bayer Corp.) *ω-Carboxyaryl subst. diphenyl ureas as raf kinase inhibitors*. WO 0042012.

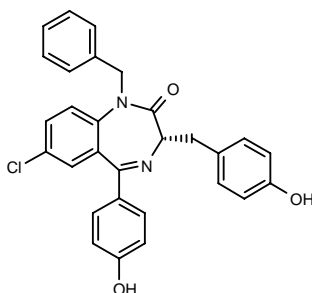
292990

1-(Biphenyl-4-ylmethyl)-7-chloro-3(*S*)-(4-hydroxybenzyl)-5-(4-hydroxyphenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one



C35 H27 Cl N2 O3; Mol wt: 559.0623

ACTION – Nonpeptide inhibitor of protein tyrosine kinases that demonstrated *in vitro* affinity and selectivity for Src kinase and showed complete inhibition of colony formation of colon adenocarcinoma HT-29 cells at 28 μ M; at the same concentration, < 10% inhibition of normal human fibroblast AFB-13 cells was observed. Another specifically claimed 1,4-benzodiazepin-2-one is:



292991: C29 H23 Cl N2 O3

SOURCES – University of California, Oakland, Oakland, CA (US); University of Texas System, Austin, TX (US).

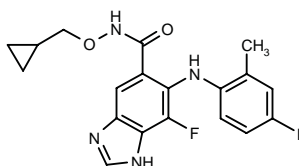
REFERENCES

1. Budde, R.J.A. et al. (University of Texas System; University of California, Oakland) *Inhibitors of protein tyrosine kinases*. US 6100254.

PD-254552

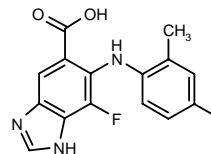
292568

N-(Cyclopropylmethoxy)-7-fluoro-6-(4-iodo-2-methylphenylamino)-1*H*-benzimidazole-5-carboxamide



C19 H18 F I N4 O2; Mol wt: 480.2752

ACTION – Selective inhibitor of MEK kinase, potentially useful for the treatment of proliferative diseases, cancer, stroke, heart failure, xenograft rejection, arthritis, cystic fibrosis, hepatomegaly, cardiomegaly, Alzheimer's disease, diabetic complications, septic shock and viral infections. Another exemplified benzoheterocyclic compound is:



PD-205293 [292569]: C15 H11 F I N3 O2

SOURCE – Pfizer.

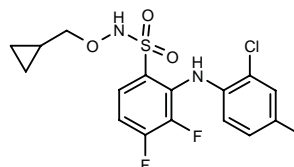
REFERENCES

1. Barrett, S.D. et al. (Warner-Lambert Co.) *Benzoheterocycles and their use as MEK inhibitors*. JP 2000204079, WO 0042022.

PD-297447

292566

2-(2-Chloro-4-iodophenylamino)-*N*-(cyclopropylmethoxy)-3,4-difluorobenzenesulfonamide



C16 H14 Cl F2 I N2 O3 S; Mol wt: 514.7126

ACTION – A representative compound from a series of sulfohydroxamic acids and sulfohydroxamates that are selective inhibitors of MEK kinase and thereby potentially useful for the treatment of proliferative diseases, cancer, stroke, heart failure, xenograft rejection, arthritis, cystic fibrosis, hepatomegaly, cardiomegaly, Alzheimer's disease, diabetic complications, septic shock and viral infections.

SOURCE – Pfizer.

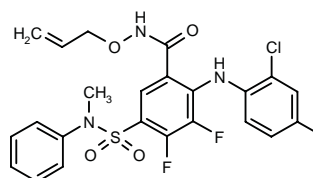
REFERENCES

1. Tecle, H. (Warner-Lambert Co.) *Sulphohydroxamic acids and sulphohydroxamates and their use as MEK inhibitors*. JP 2000204075, WO 0042002.

PD-298459

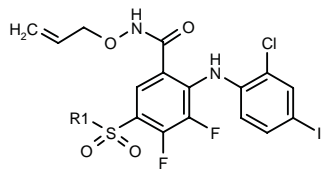
292570

N-Allyloxy-2-(2-chloro-4-iodophenylamino)-3,4-difluoro-5-(*N*-methyl-*N*-phenylsulfamoyl)benzamide



C23 H19 Cl F2 I N3 O4 S; Mol wt: 633.8351

ACTION – Selective inhibitor of MEK kinase, potentially useful for the treatment of proliferative diseases, cancer, stroke, heart failure, xenograft rejection, arthritis, cystic fibrosis, hepatomegaly, cardiomegaly, Alzheimer’s disease, diabetic complications, septic shock and viral infections. Other exemplified benzenesulfonamide derivatives are:



Compound	R1	Formula
PD-298458 [292571]	4-Me-1-Piz	C ₂₁ H ₂₂ ClF ₂ IN ₄ O ₄ S
PD-298460 [292572]	allyl-N(Me)	C ₂₀ H ₁₉ ClF ₂ IN ₃ O ₄ S
PD-298463 [292573]	3-(NH ₂ CO)-1-Pip	C ₂₂ H ₂₂ ClF ₂ IN ₄ O ₅ S
PD-298464 [292574]	N(Me)(CH ₂) ₃ N(Me) ₂	C ₂₂ H ₂₆ ClF ₂ IN ₄ O ₄ S
PD-298465 [292575]	4-(2-Pyr)-1-Piz	C ₂₅ H ₂₃ ClF ₂ IN ₃ O ₄ S
PD-298467 [292576]	N(Me)OMe	C ₁₈ H ₁₇ ClF ₂ IN ₃ O ₅ S

SOURCE – Pfizer.

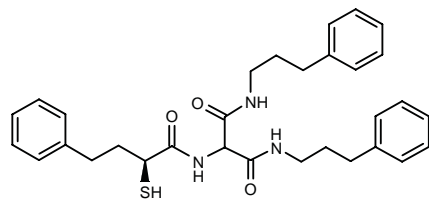
REFERENCES

1. Barrett, S.D. et al. (Warner-Lambert Co.) *Benzenesulfonamide derivs. and their use as MEK inhibitors*. JP 2000212157, WO 0042003.

ANGIOGENESIS INHIBITORS

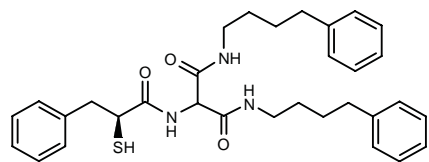
292366

*N*¹,*N*³-Bis(3-phenylpropyl)-2-[4-phenyl-2(*S*)-sulfanylbutyramido]malonamide



C31 H37 N3 O3 S; Mol wt: 531.7173

ACTION – Matrix metalloproteinase (MMP) inhibitor expected to be useful for the treatment of neoplastic diseases, rheumatoid arthritis, osteoporosis and chronic inflammatory disorders such as emphysema. Another specifically claimed amidomalonamide is:



292367: C32 H39 N3 O3 S

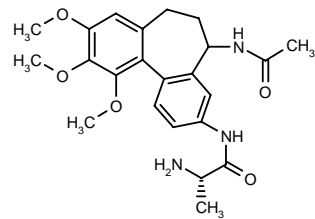
SOURCE – Aventis Pharma.

REFERENCES

1. Warshawsky, A. and Janusz, M.J. (Aventis Pharmaceuticals, Inc.) *Amidomalonamides and their use as inhibitors of matrix metalloproteinase*. WO 0040552.

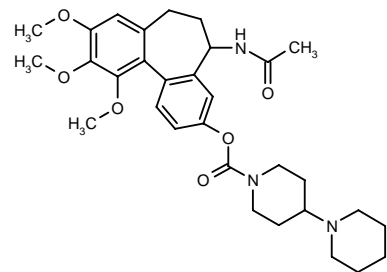
292441

*N*¹-(5-Acetamido-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl)-L-alaninamide



C23 H29 N3 O5; Mol wt: 427.4981

ACTION – Vascular damaging agent that specifically damages newly formed vasculature without affecting the normal established vascular endothelium. The compound produced a decrease in tumor functional vascular volume in CaNT tumor-bearing mice. Potentially useful for the treatment of angiogenesis-related diseases such as cancer and rheumatoid arthritis. Another exemplified colchicol derivative is:



292442: C31 H41 N3 O6

SOURCE – Angiogene Pharmaceuticals.

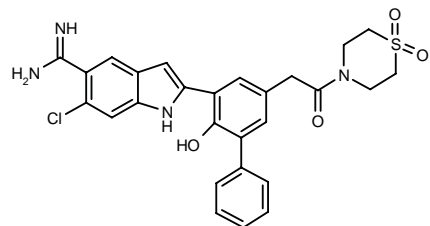
REFERENCES

1. Davis, P.D. et al. (Angiogene Pharmaceuticals Ltd.) *Colchicol derivs. as vascular damaging agents*. WO 0040529.

OTHER ONCOLYTIC DRUGS

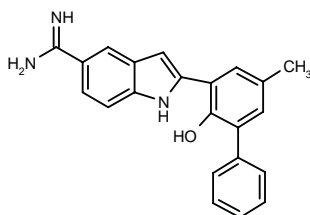
291712

6-Chloro-2-[5-[2-(1,1-dioxothiophorolin-4-yl)-2-oxoethyl]-2-hydroxybiphenyl-3-yl]-1*H*-indole-5-carboxamidine



C27 H25 Cl N4 O4 S; Mol wt: 537.0375

ACTION – Serine protease inhibitor with selectivity for urokinase ($K_i = 0.004$ and $5.4 \mu\text{M}$ for urokinase-type plasminogen activator [uPA] and factor Xa, respectively), potentially useful for the treatment of cancer. Another exemplified compound is:



291713: C22 H19 N3 O

The invention also includes selective factor Xa inhibitors useful as anticoagulants (see **291714**).

SOURCE – Axys Pharmaceuticals.

REFERENCES

1. Allen, D.A. et al. (Axys Pharmaceuticals, Inc.) *Protease inhibitors*. WO 0035886.

BEXAROTENE⁺

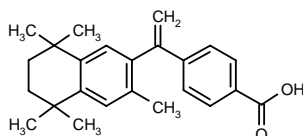
New formulation

214151

4-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)vinyl]benzoic acid

LG-100069

LGD-1069



C24 H28 O2; Mol wt: 348.4900

Fine white crystals, m.p. 234 °C.

ACTION – Retinoid X receptor (RXR)-selective retinoid that activates RXR α , RXR β and RXR γ receptors and shows antiproliferative activity against certain tumor cell lines.

INDICATION – Treatment of cutaneous lesions in patients with early-stage cutaneous T-cell lymphoma.

PRESENTATION – Gel, 1%.

PROPRIETARY NAME – Targretin (US).

SOURCE – Ligand.

REFERENCES

1. Breneman, D.L. et al. *Phase 1-2 clinical trial supports the safety and efficacy of Targretin™ topical gel, a novel RXR-selective retinoid analogue, in the treatment of cutaneous T-cell lymphoma*. Blood 1996, 88(10, Suppl. 1): Abst 2265.

2. Alfa Wassermann will market and distribute Ligand's oncology products in Italy. DailyDrugNews.com (Daily Essentials) 2000, Jan 12.

3. FDA approves Targretin gel for treatment of cutaneous T-cell lymphoma. DailyDrugNews.com (Daily Essentials) 2000, June 30.

4. Investigators present interim phase I/II data on Targretin™ (LGD1069) topical in cutaneous T-cell lymphoma at American Society of Hematology Conference. 41% of patients achieve partial or complete response. Ligand Pharmaceuticals Press Release 1996, Dec 9.

5. Ligand receives approvable letter from FDA for Targretin Gel. DailyDrugNews.com (Daily Essentials) 2000, June 15.

6. Ligand reports data from two trials of Targretin gel formulation in CTCL. DailyDrugNews.com (Daily Essentials) 2000, May 17.

7. Ligand submits NDA for Targretin Gel as CTCL therapy. DailyDrugNews.com (Daily Essentials) 1999, Dec 14.

8. Ligand to launch three pivotal trials with Targretin™ (LGD1069) oral and topical. Ligand Pharmaceuticals Press Release 1996, Aug 22.

9. Ligand updates market on Targretin™ (LGD1069) topical at Hambrecht & Quist Life Sciences Conference. Ligand Pharmaceuticals Press Release 1996, Jan 5.

10. Ligand updates product development programs. DailyDrugNews.com (Daily Essentials) 2000, May 24.

11. Targretin gel formulation granted priority review status. DailyDrugNews.com (Daily Essentials) 2000, Feb 9.

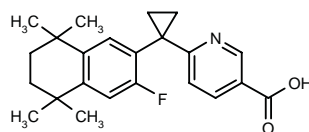
12. Topical formulation of Targretin launched in U.S. for CTCL therapy. DailyDrugNews.com (Daily Essentials) 2000, Sept 28.

*The capsule formulation was previously launched, see Drug Data Rep 2000, 022(04): 0375.

L-007²

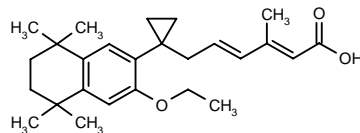
292494

6-[1-(3-Fluoro-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]pyridine-3-carboxylic acid



C23 H26 F N O2; Mol wt: 367.4614

ACTION – Retinoic acid receptor RXR α -selective ligand ($\text{IC}_{50} = 15 \text{ nM}$), potentially useful for the treatment of breast cancers that have developed resistance to antihormonal therapies such as tamoxifen. Another RXR-selective ligand is:



L-015 [292495]^{1,2}: C26 H36 O3

SOURCE – Ligand.

REFERENCES

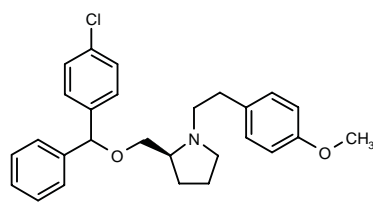
1. Farmer, L.J. and Zhi, L. (Ligand Pharmaceuticals, Inc.) *Retinoids, methods for their production and use*. US 6005007.

2. Michellys, P.-Y. et al. *Use of RXR-selective ligands in chemoprevention and chemotherapy of carcinomas*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 192.

TH-1177

282770

2(S)-[[[(4-Chlorophenyl)(phenyl)methoxy]methyl]-1-[2-(4-methoxyphenyl)ethyl]pyrrolidine



C27 H30 Cl N O2; Mol wt: 435.9920

ACTION – Antineoplastic agent proven to block the influx of extracellular Ca²⁺ in susceptible cancer cells including prostate LNCaP and PC-3 cells (IC₅₀ = 3 and 16 μM, respectively). At concentrations similar to those which block Ca²⁺ entry in these two cell types, compound also inhibited cell proliferation (ED₅₀ = 4 and 14 μM, in LNCaP and PC-3 cells, respectively) via a cytostatic mechanism. In a murine model of human prostate cancer PC-3, it significantly increased the lifespan by 38% at 10 mg/kg/day i.p. for 50 days. Compound did not show systemic toxicity at a daily dose of 180 mg/kg i.p. for 22 days in SCID mice.

SOURCE – University of Virginia, Charlottesville, VA (US).

REFERENCES

1. Haverstick, D.M. et al. *Inhibition of human prostate cancer proliferation in vitro and in a mouse model by a compound synthesized to block Ca²⁺ entry*. Cancer Res 2000, 60(4): 1002.

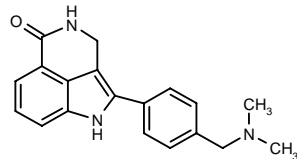
2. Havrstick, D.M. et al. *Inhibition of human prostate cancer proliferation in vitro and in a mouse model by a compound synthesized to block Ca²⁺ entry*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington DC) 1999, Abst 361.

3. Heady, T.N. et al. *Synthesis and structure-activity relationship (SAR) of novel calcium channel blockers*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 73.

MODULATORS OF THE
THERAPEUTIC ACTIVITY OF
ANTINEOPLASTIC AGENTS

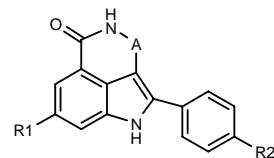
292524

2-[4-(Dimethylaminomethyl)phenyl]-1,3,4,5-tetrahydro-pyrrolo[4,3,2-*de*]isoquinolin-5-one



C19 H19 N3 O; Mol wt: 305.3791

ACTION – Poly(ADP-ribose)polymerase (PARP, NAD⁺ ADP-ribosyltransferase) inhibitor (K_i = 0.7-1 nM) potentially useful in the treatment of cancer, preferably in combination with DNA-damaging cytotoxic drugs, as well as for the therapy of stroke, head trauma and neurodegenerative diseases. The compound exhibited a potentiation factor (PF₅₀; ratio of the IC₅₀ of topotecan alone to the IC₅₀ of topotecan in combination with the test compound) of 2.2 in human lung carcinoma A549 cells. Other exemplified tricyclic compounds include the following:



Compound	R1	R2	A	Formula
292525	H	Cl	-N=CH-	C ₁₆ H ₁₀ ClN ₃ O
292526	F	CH2NHMe	-(CH2)2-	C ₁₉ H ₁₈ FN ₃ O

SOURCES – Agouron (Pfizer); Cancer Research Campaign Technology.

REFERENCES

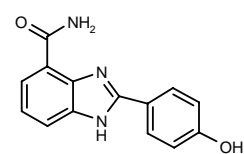
1. Webber, S.E. et al. (Agouron Pharmaceuticals, Inc.;Cancer Research Campaign Technology Ltd.) *Tricyclic inhibitors of poly(ADP-ribose) polymerases*. WO 0042040.

2. Tikhe, J.G. et al. *Synthesis and study of novel tricyclic inhibitors of poly(ADP-ribose)polymerase*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 74.

NU-1085

274497

2-(4-Hydroxyphenyl)-1*H*-benzimidazole-4-carboxamide



C14 H11 N3 O2; Mol wt: 253.2599

ACTION – Poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferas) inhibitor (K_i = 6 nM) proven to potentiate the growth-inhibitory effect of temozolomide or topotecan against a panel of human tumor cell lines including lung, colon, ovarian and breast cancer cells, independent of p53 status; compound also potentiated the cytotoxicity of these compounds. Potentially useful for modulating drug resistance for use in chemo- and radiopotentialiation strategies.

SOURCES – Agouron (Pfizer); University of Newcastle upon Tyne, Newcastle upon Tyne (GB).

REFERENCES

1. Griffin, R.J. et al. (University of Newcastle upon Tyne) *Benzimidazole cpds*. US 6100283.

2. Calabrese, C.R. et al. *Pharmacokinetics and tissue distribution of novel potent inhibitors of poly(ADP-ribose) polymerase (PARP)*. Proc Amer Assoc Cancer Res 1999, 40: Abst 2578.

3. Calabrese, C.R. et al. *Preclinical pharmacology of novel substituted benzimidazoles - Potent inhibitors of poly (ADP-ribose) polymerase*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington DC) 1999, Abst 543.

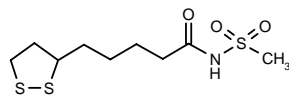
4. Delaney, C.A. et al. *Potentialiation of temozolomide and topotecan growth inhibition and cytotoxicity by novel poly(adenosine diphosphoribose) polymerase inhibitors in a panel of human tumor cell lines*. Clin Cancer Res 2000, 6(7): 2860.

5. White, A.W. et al. *Resistance-modifying. 9. Synthesis and biological properties of benzimidazole inhibitors of the DNA repair enzyme poly (ADP-ribose) polymerase*. J Med Chem 2000, 43(22): 4084.

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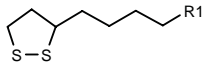
292080

5-(1,2-Dithiolan-3-yl)-N-(methylsulfonyl)pentanamide



C9 H17 N O3 S3; Mol wt: 283.4353

ACTION – Anticataract agent that potentiates the activity of glutathione reductase. The compound is also potentially useful as a radioprotectant and chemoprotectant. Other exemplified dithiolane derivatives are:



Compound	R1	Formula
292081	CONHSO2NH2	C ₈ H ₁₆ N ₂ O ₃ S ₃
292082	NHCONHMe	C ₉ H ₁₈ N ₂ OS ₂

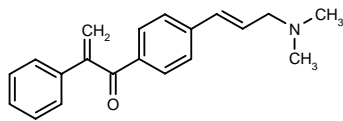
SOURCE – Sankyo.

REFERENCES

1. Fujita, T. and Yokoyama, T. (Sankyo Co., Ltd.) *Medicines containing dithiolane derivs*. JP 2000169371.

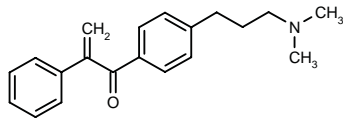
292504

1-[4-[3-(Dimethylamino)-1(E)-propenyl]phenyl]-2-phenyl-2-propen-1-one



C20 H21 N O; Mol wt: 291.3919

ACTION – Agent for the treatment of glaucoma reported to lower intraocular pressure by inducing a morphological change in trabecular cells. Another exemplified 1,2-diphenyl-2-propen-1-one derivative is:



292505: C20 H23 N O

SOURCE – Santen.

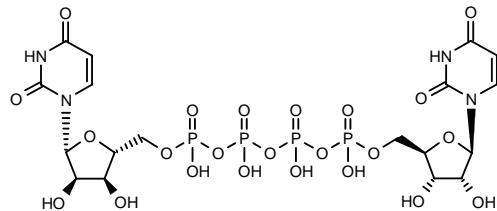
REFERENCES

1. Shirasawa, E. et al. (Santen Pharmaceutical Co., Ltd.) *Novel 1,2-diphenyl-2-propen-1-one derivs*. WO 0041993.

INS-365

263630

P1,P4-Di(uridine-5'-tetraphosphate)



C18 H26 N4 O23 P4; Mol wt: 790.3044

ACTION – Potent purine P2Y₂ receptor agonist (EC₅₀ = 0.02 µM) proven to induce significant and dose-related increases in mucociliary clearance of the airways in sheep following inhalation, as well as to enhance tear secretion in rabbits when administered as eye drops. Potentially useful for the treatment of chronic bronchitis, cystic fibrosis and dry eye disease. Compound is undergoing phase IIb trials for the treatment of dry eye disease.

SOURCES – Genentech; Inspire Pharmaceuticals; Kissei; University of North Carolina, Chapel Hill, NC (US); Santen.

REFERENCES

1. Lacroix, K.K. et al. (Inspire Pharmaceuticals, Inc.) *Method of early lung cancer detection via sputum induction and analysis of sputum to detect cancer associated substances*. WO 9815835.

2. Pendergast, W. et al. (Inspire Pharmaceuticals, Inc.) *Certain dinucleotides and their use as modulators of mucociliary clearance and ciliary beat frequency*. WO 9834942.

3. Pendergast, W. et al. (Inspire Pharmaceuticals, Inc.) *Method of promoting cervical and vaginal secretions*. WO 0030629.

4. Shaffer, C.L. et al. (Inspire Pharmaceuticals, Inc.) *Method of treating bronchitis with uridine triphosphates and related cpds*. WO 9819685.

5. Stutts, M.J. III et al. (University of North Carolina) *Dinucleotides useful for hydrating lung mucous secretions*. US 5935555.

6. Yerxa, B.J. and Pendergast, W. (Inspire Pharmaceuticals, Inc.) *Method for large-scale production of di(uridine 5'-tetraphosphate) and salts thereof*. WO 9905155.

7. Dougherty, R.W. et al. *Effects of INS365, a P2Y2 receptor agonist, on components of the mucociliary clearance system*. Pediatr Pulmonol 1998, (Suppl. 17): Abst 282.

8. Mao, Y.M. et al. *Aerosolization of P2Y2 agonists, uridine 5'-triphosphate (UTP) and INS365 induces a dose related increase in tracheal mucus velocity (TMV) in sheep*. Am J Respir Crit Care Med 1998, 157(3): A366.

9. Shaffer, C.L. et al. *INS365, a novel P2Y2 receptor agonist and ion channel modulator for the treatment of cystic fibrosis: Results from initial phase I study*. Pediatr Pulmonol 1998, (Suppl. 17): Abst 198.

10. Shaver, S.R. et al. *Synthesis and SAR of P2Y2 receptor agonists*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MED1 188.

11. Yerxa, B.R. *Therapeutic use of nucleotides in respiratory and ophthalmic diseases*. Drug Dev Res 2000, 50(1): Abst S14-04.

12. Yerxa, B.R. and Johnson, F.L. *P2Y2 receptors agonists: Structure, activity and therapeutic utility*. Drugs Fut 1999, 24(7): 0759.

13. Yerxa, B.R. et al. *INS365, a P2Y2 receptor agonist, increases Schirmer scores in albino rabbits*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 2848.

3. Calabrese, C.R. et al. *Preclinical pharmacology of novel substituted benzimidazoles - Potent inhibitors of poly (ADP-ribose) polymerase*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington DC) 1999, Abst 543.

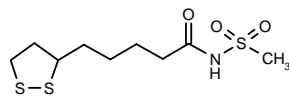
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OCULAR MEDICATIONS

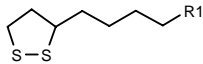
292080

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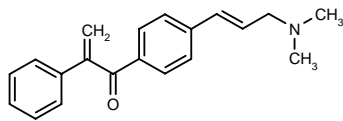
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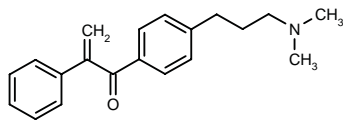
292504

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292505: C20 H23 N O

SOURCE – Santen.

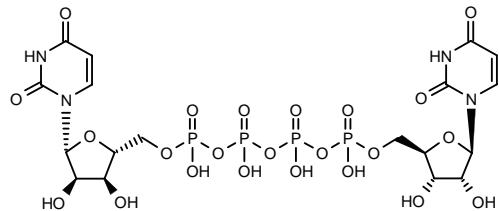
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263630

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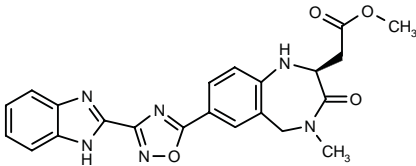
14. *Genentech and Inspire enter respiratory therapeutics collaboration.* DailyDrugNews.com (Daily Essentials) 1999, Dec 27.
15. *Inspire presents positive results for dry eye disease therapeutic.* DailyDrugNews.com (Daily Essentials) 1999, May 13.
16. *Inspire's dry eye product enters phase II testing.* DailyDrugNews.com (Daily Essentials) 2000, Jan 10.
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18. *Inspire reports progress in third quarter.* DailyDrugNews.com (Daily Essentials) 2000, Nov. 11.
19. *Inspire updates product development during BIO-Europe.* DailyDrugNews.com (Daily Essentials) 2000, Nov 22.
20. *Ophthalmic INS-365 to be developed by Inspire in collaboration with Santen.* DailyDrugNews.com (Daily Essentials) 1999, Jan 5.
21. *Positive phase I safety and efficacy results reported for INS-365.* DailyDrugNews.com (Daily Essentials) 1998, Oct 20.
22. *Positive phase II results reported for INS-365 as dry eye disease treatment.* DailyDrugNews.com (Daily Essentials) 2000, Nov 14.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

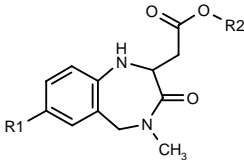
291741

2-[7-[3-(1*H*-Benzimidazol-2-yl)-1,2,4-oxadiazol-5-yl]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-2(S)-yl]acetic acid methyl ester



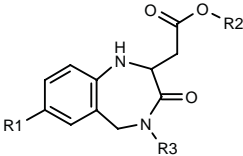
C22 H20 N6 O4; Mol wt: 432.4380

ACTION – Integrin antagonist, particularly active at the $\alpha_v\beta_3$ and/or the $\alpha_v\beta_5$ receptor, with a good kinetic profile and a broad spectrum of activity. Potentially useful for the treatment of osteoporosis, restenosis, cancer and atherosclerosis. Other exemplified 1,4-benzodiazepinone derivatives are:



Compound	R1	R2	Isomer	Formula
291742	3-(2-benzimidazolyl)- -1,2,4-oxadiazol-5-yl	H	S	C ₂₁ H ₁₈ N ₆ O ₄
291743	5-(2-benzimidazolyl)- -1,3,4-oxadiazol-2-yl	Me		C ₂₂ H ₂₀ N ₆ O ₄
291744	5-(2-benzimidazolyl)- -1,3,4-oxadiazol-2-yl	H		C ₂₁ H ₁₈ N ₆ O ₄
291745	5-(2-benzimidazolyl)- -1,3,4-thiadiazol-2-yl	Me		C ₂₂ H ₂₀ N ₆ O ₃ S

Compound	R1	R2	Isomer	Formula
291746	5-(2-benzimidazolyl)- -1,3,4-thiadiazol-2-yl	H		C ₂₁ H ₁₈ N ₆ O ₃ S
291747	4-(2-benzimidazolyl)- -4,5-dihydro-2-oxazolyl	Me		C ₂₃ H ₂₃ N ₆ O ₄
291748	4-(2-benzimidazolyl)- -4,5-dihydro-2-oxazolyl	H		C ₂₂ H ₂₁ N ₆ O ₄
291749	3-(6-NO2-2-benzimidazolyl)- -1,2,4-oxadiazol-5-yl	Me	S	C ₂₂ H ₁₉ N ₇ O ₆
291750	3-(5-NO2-2-benzimidazolyl)- -1,2,4-oxadiazol-5-yl	H	S	C ₂₁ H ₁₇ N ₇ O ₆



Compound	R1	R2	R3	Formula
291751	3-(2-benzimidazolyl)- -1,2,4-oxadiazol-5-yl	Me	cyclopropyl	C ₂₄ H ₂₂ N ₆ O ₄
291752	3-(2-benzimidazolyl)- -1,2,4-oxadiazol-5-yl	H	cyclopropyl	C ₂₃ H ₂₀ N ₆ O ₄
291753	5-(2-benzimidazolyl)- -1,3,4-thiadiazol-2-yl	Me	CH2CH2OMe	C ₂₄ H ₂₄ N ₆ O ₄ S
291754	5-(2-benzimidazolyl)- -1,3,4-oxadiazol-2-yl	H	CH2CH2OMe	C ₂₃ H ₂₂ N ₆ O ₅

SOURCE – Bayer.

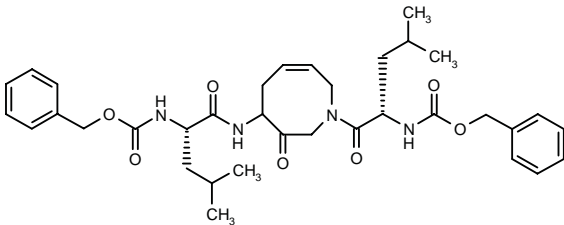
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292262

N-[1(*S*)-[4-(*N*-Benzyloxycarbonyl-L-leucylamino)-3-oxo-1,2,3,4,5,8-hexahydroazocin-1-ylcarbonyl]-3-methyl-butyl]carbamic acid benzyl ester

*N*²-(Benzyloxycarbonyl)-*N*¹-[1-[*N*-(benzyloxycarbonyl)-L-leucyl]-3-oxo-1,2,3,4,5,8-hexahydroazocin-4-yl]-L-leucinamide



C35 H46 N4 O7; Mol wt: 634.7694

ACTION – Cysteine and serine protease inhibitor, particularly active against cathepsin K, potentially useful in treating diseases of excessive bone loss and cartilage or matrix degradation including osteoporosis, periodontitis, gingivitis, osteoarthritis, rheumatoid arthritis, Paget's disease, hypercalcemia of malignancy and metabolic bone disease. Other specifically claimed compounds are:

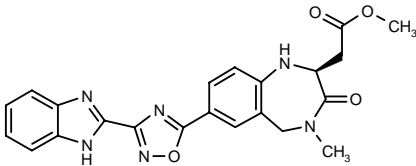
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

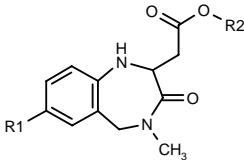
291741

2-[7-[3-(1*H*-Benzimidazol-2-yl)-1,2,4-oxadiazol-5-yl]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-2(S)-yl]acetic acid methyl ester



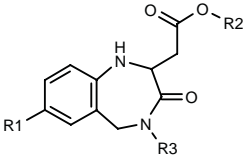
C22 H20 N6 O4; Mol wt: 432.4380

ACTION – Integrin antagonist, particularly active at the $\alpha_v\beta_3$ and/or the $\alpha_v\beta_5$ receptor, with a good kinetic profile and a broad spectrum of activity. Potentially useful for the treatment of osteoporosis, restenosis, cancer and atherosclerosis. Other exemplified 1,4-benzodiazepinone derivatives are:



Compound	R1	R2	Isomer	Formula
291742	3-(2-benzimidazolyl)-1,2,4-oxadiazol-5-yl	H	S	C ₂₁ H ₁₈ N ₆ O ₄
291743	5-(2-benzimidazolyl)-1,3,4-oxadiazol-2-yl	Me		C ₂₂ H ₂₀ N ₆ O ₄
291744	5-(2-benzimidazolyl)-1,3,4-oxadiazol-2-yl	H		C ₂₁ H ₁₈ N ₆ O ₄
291745	5-(2-benzimidazolyl)-1,3,4-thiadiazol-2-yl	Me		C ₂₂ H ₂₀ N ₆ O ₃ S

Compound	R1	R2	Isomer	Formula
291746	5-(2-benzimidazolyl)-1,3,4-thiadiazol-2-yl	H		C ₂₁ H ₁₈ N ₆ O ₃ S
291747	4-(2-benzimidazolyl)-4,5-dihydro-2-oxazolyl	Me		C ₂₃ H ₂₃ N ₆ O ₄
291748	4-(2-benzimidazolyl)-4,5-dihydro-2-oxazolyl	H		C ₂₂ H ₂₁ N ₆ O ₄
291749	3-(6-NO2-2-benzimidazolyl)-1,2,4-oxadiazol-5-yl	Me	S	C ₂₂ H ₁₉ N ₇ O ₆
291750	3-(5-NO2-2-benzimidazolyl)-1,2,4-oxadiazol-5-yl	H	S	C ₂₁ H ₁₇ N ₇ O ₆



Compound	R1	R2	R3	Formula
291751	3-(2-benzimidazolyl)-1,2,4-oxadiazol-5-yl	Me	cyclopropyl	C ₂₄ H ₂₂ N ₆ O ₄
291752	3-(2-benzimidazolyl)-1,2,4-oxadiazol-5-yl	H	cyclopropyl	C ₂₃ H ₂₀ N ₆ O ₄
291753	5-(2-benzimidazolyl)-1,3,4-thiadiazol-2-yl	Me	CH2CH2OMe	C ₂₄ H ₂₄ N ₆ O ₄ S
291754	5-(2-benzimidazolyl)-1,3,4-oxadiazol-2-yl	H	CH2CH2OMe	C ₂₃ H ₂₂ N ₆ O ₅

SOURCE – Bayer.

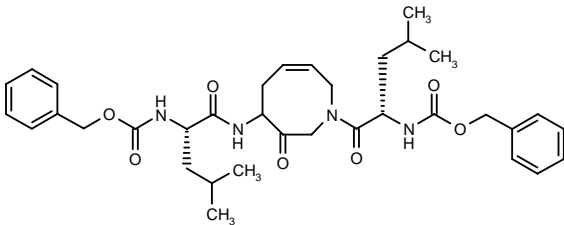
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292262

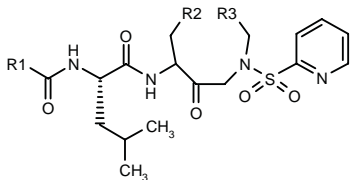
N-[1(*S*)-[4-(*N*-Benzyloxycarbonyl-L-leucylamino)-3-oxo-1,2,3,4,5,8-hexahydroazocin-1-ylcarbonyl]-3-methylbutyl]carbamic acid benzyl ester

*N*²-(Benzyloxycarbonyl)-*N*¹-[1-[*N*-(benzyloxycarbonyl)-L-leucyl]-3-oxo-1,2,3,4,5,8-hexahydroazocin-4-yl]-L-leucinamide

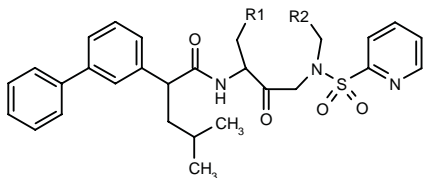


C35 H46 N4 O7; Mol wt: 634.7694

ACTION – Cysteine and serine protease inhibitor, particularly active against cathepsin K, potentially useful in treating diseases of excessive bone loss and cartilage or matrix degradation including osteoporosis, periodontitis, gingivitis, osteoarthritis, rheumatoid arthritis, Paget's disease, hypercalcemia of malignancy and metabolic bone disease. Other specifically claimed compounds are:



Compound	R1	R2,R3	Formula
292263	2-benzofuryl	-CH=CH-	C ₂₇ H ₃₀ N ₄ O ₆ S
292266	2-quinolyl	-(CH ₂) ₂ -	C ₂₈ H ₃₃ N ₅ O ₅ S
292267	2-quinolyl	-CH=CH-	C ₂₈ H ₃₁ N ₅ O ₅ S
292268	2-benzofuryl	-(CH ₂) ₂ -	C ₂₇ H ₃₂ N ₄ O ₆ S
292269	2-benzothieryl	-(CH ₂) ₂ -	C ₂₇ H ₃₂ N ₄ O ₅ S ₂
292270	2-benzothieryl	-CH=CH-	C ₂₇ H ₃₀ N ₄ O ₅ S ₂



Compound	R1,R2	Formula
292264	-(CH ₂) ₂ -	C ₃₀ H ₃₅ N ₃ O ₄ S
292265	-CH=CH-	C ₃₀ H ₃₃ N ₃ O ₄ S

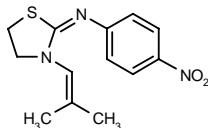
SOURCE – SmithKline Beecham.

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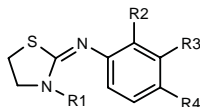
292633

N-[3-(2-Methyl-1-propenyl)thiazolidin-2-ylidene]-N-(4-nitrophenyl)amine



C13 H15 N3 O2 S; Mol wt: 277.3465

ACTION – Nonsteroidal progesterone receptor ligand found to produce 80-100% inhibition of [³H]-progesterone binding to the progesterone receptor at 200 nM. The compound is expected to be useful in a wide range of disorders including osteoporosis or osteopenia and gynecological disorders. Other representative compounds from this series of 2-arylimino or 2-heteroarylimino heterocycles are:



Compound	R1	R2	R3	R4	Formula
292634	i-Bu	Me	H	NO ₂	C ₁₄ H ₁₉ N ₃ O ₂ S
292635	CH ₂ CH(Me)Et	Me	H	NO ₂	C ₁₅ H ₂₁ N ₃ O ₂ S
292636	vinyl-(CH ₂) ₆	Me	H	NO ₂	C ₁₈ H ₂₅ N ₃ O ₂ S
292637	CH ₂ CH=C(Cl) ₂	Me	H	NO ₂	C ₁₃ H ₁₃ Cl ₂ N ₃ O ₂ S
292638	cyclooctyl	OMe	H	NO ₂	C ₁₈ H ₂₅ N ₃ O ₃ S
292639	cyclohexyl-CH ₂	Cl	Cl	H	C ₁₆ H ₂₀ Cl ₂ N ₂ S

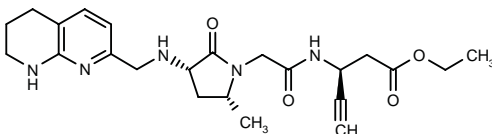
SOURCE – Bayer.

REFERENCES

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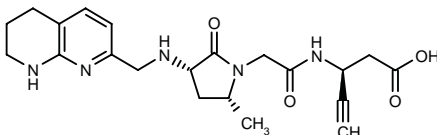
292692

3(S)-[2-[5(R)-Methyl-2-oxo-3(S)-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-ylmethylamino)pyrrolidin-1-yl]-acetamido]-4-pentynoic acid ethyl ester



C23 H31 N5 O4; Mol wt: 441.5289

ACTION – Agent for the treatment of osteoporosis, the ethyl ester prodrug of a pyrrolidinone-containing vitronectin $\alpha_v\beta_3$ receptor antagonist (**292691**). Compound showed good oral bioavailability (21%) and a half-life of 2 h in dogs. In ovariectomized rats, doses of 20 and 30 mg/kg b.i.d. for 28 days suppressed the loss of bone mineral density and bone volume seen in controls.



292691: C21 H27 N5 O4

SOURCE – Merck & Co.

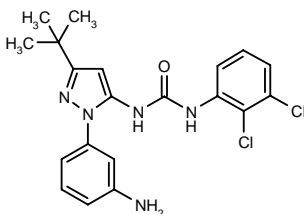
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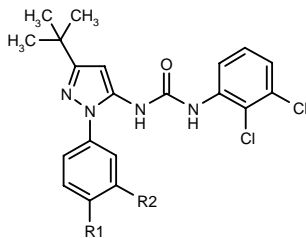
292758

N-[1-(3-Aminophenyl)-3-tert-butyl-1H-pyrazol-5-yl]-N'-(2,3-dichlorophenyl)urea



C20 H21 Cl2 N5 O; Mol wt: 418.3259

ACTION – Potent p38 kinase inhibitor with IC₅₀ values of 13 and 52 nM against the p38α2 and p38β1 isoforms, respectively. Compound showed good selectivity relative to other kinases, including JNK-1, abl, HER-2 and p56^{lck} (IC₅₀ = 850 nM or greater), and no activity against ERK-1, protein kinase A or C, p59^{lyn} and epidermal growth factor (EGF) receptor kinase. Compound strongly inhibited IL-6 production induced by TNF-α/IL-1 in SW1353 cells (IC₅₀ = 42 nM), as well as TNF-α production induced by lipopolysaccharide in human peripheral blood mononuclear cells (IC₅₀ = 99 nM). *In vivo*, compound given orally at doses of 50 and 100 mg/kg was seen to significantly reduce IL-6 production induced by TNF-α or endotoxin in mice. Potentially useful for the treatment of endotoxic shock, bone resorption and arthritis. Within this series of urea analogues, the following are also described:



Compound	R1	R2	Formula
292757	H	NO2	C ₂₀ H ₁₉ Cl ₂ N ₅ O ₃
292759	SO2Me	H	C ₂₁ H ₂₂ Cl ₂ N ₄ O ₃ S

SOURCE – Bayer.

REFERENCES

1. Dumas, J. et al. (Bayer AG) *Inhibition of p38 kinase activity using aryl and heteroaryl substd. heterocyclic ureas*. WO 9932110.

2. Dumas, J. et al. *1-Phenyl-5-pyrazolyl ureas: Potent and selective p38 kinase inhibitors*. Bioorg Med Chem Lett 2000, 10(18): 2051.

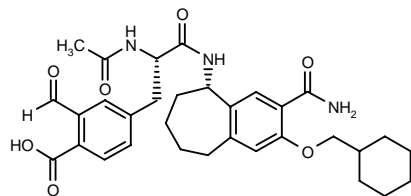
3. Dumas, J. et al. *Synthesis and SAR of p38 kinase inhibitors from the urea class*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 148.

4. Ranges, G.E. et al. *Pharmacological characterization of pyrazolyl urea p38 kinase inhibitors*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 149.

AP-22161*

289969

4-[2 (S)-Acetamido-3-[3-carbamoyl-2-(cyclohexylmethoxy)-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5(S)-ylamino]-3-oxopropyl]-2-formylbenzoic acid



C32 H39 N3 O7; Mol wt: 577.6741

ACTION – An inhibitor of Src protein tyrosine kinase that selectively binds to the Src SH2 domain (IC₅₀ = 0.24 μM) by targeting a cysteine residue with the highly conserved phosphotyrosine-binding pocket. In a cell-based assay in two hybrid cell lines expressing the secreted alkaline phosphatase (SEAP) reporter gene, compound was seen to inhibit SEAP expression with IC₅₀ values of 60.0-80.1 μM. In addition, compound was seen to block Src cellular activity, as demonstrated by inhibition of the growth of rat fibroblasts transformed with mutant cSrcY527F, as well as to inhibit rabbit osteoclast-mediated resorption of dentine with an IC₅₀ value of 42.92 μM. Prototype lead compound for further development as a potential agent for the treatment of osteoporosis.

SOURCE – Ariad.

REFERENCES

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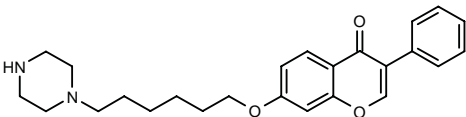
2. Violette, S.M. et al. *A Src SH2 selective binding compound inhibits osteoclast-mediated resorption*. Chem Biol 2000, 7(3): 255.

*Identified compound **289969** (see **289968**) Drug Data Rep 2000, 022(09): 0838.

CHF-3142

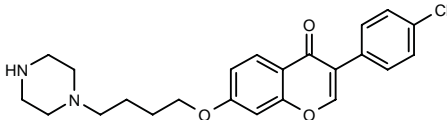
293376

3-Phenyl-7-[6-(1-piperazinyl)hexyloxy]-4H-1-benzopyran-4-one



C25 H30 N2 O3; Mol wt: 406.5230

ACTION – Agent for the treatment of osteoporosis, a novel isoflavone derivative proven to inhibit bone resorption induced by bovine parathyroid hormone fragment 1-34 *in vitro* and to completely prevent bone resorption in an ovariectomized rat model at the dose of 50 mg/kg/day p.o. Another related compound is:



CHF-3150 [293378]: C23 H25 Cl N2 O3

SOURCE – Chiesi.

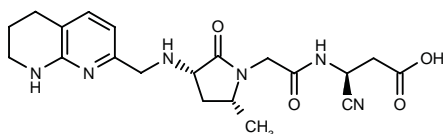
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L-806977

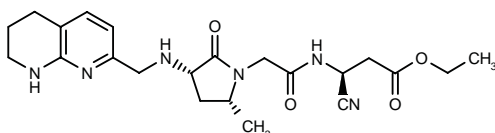
292459

3(*S*)-Cyano-3-[2-[5(*R*)-methyl-2-oxo-3(*S*)-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-ylmethylamino)pyrrolidin-1-yl]acetamido]propionic acid



C20 H26 N6 O4; Mol wt: 414.4634

ACTION – Potent and selective $\alpha_v\beta_3$ integrin antagonist ($IC_{50} = 0.31$ nM), a low-molecular-weight RGD peptidomimetic potentially useful for the treatment and prevention of osteoporosis. In attachment assays in HEK293 cells transfected with either $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin, compound inhibited integrin-mediated attachment to vitronectin with respective IC_{50} values of 3.9 and 32 nM. In addition, it inhibited murine osteoclast formation and rabbit osteoclast-mediated bone resorption with IC_{50} values of 26 and 56 nM, respectively. The ethyl ester prodrug **L-806978** prevented bone loss without inducing pathological changes in other tissues when given orally to ovariectomized rats at doses of 3, 10 and 30 mg/kg b.i.d. for 4 weeks. The prodrug at doses of 10 and 30 mg/kg p.o. induced an increase in bone mineral density of distal femur and an increase in bone volume of proximal tibia, without reducing osteoclast number on the bone surface and having no effect on the femoral osteoclast surface.



L-806978 [292814]: C22 H30 N6 O4

SOURCE – Merck & Co.

REFERENCES

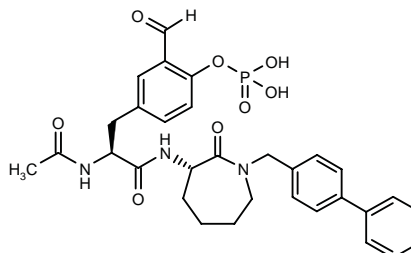
1. Duggan, M.E. et al. *Design and synthesis of potent $\alpha_v\beta_3$ antagonists: Discovery of 5,6,7,8-tetrahydro[1,8]naphthyridine as a lipophilic, moderately basic guanidine replacement*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 166.

2. Rodan, S.B. et al. *An oral antagonist of $\alpha_v\beta_3$ integrin prevents bone loss in ovariectomized rats*. 22nd Annu Meet Am Soc Bone Miner Res (ASBMR) (Sept 22-26, Toronto) 2000, Abst SA374.

RU-84687²

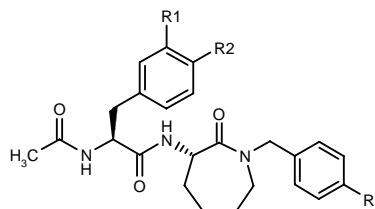
293480

*N*²-Acetyl-*N*¹-[1-(biphenyl-4-ylmethyl)-2-oxo-perhydroazepin-3(*S*)-yl]-3-formyl-4-*O*-phosphono-L-tyrosinamide



C31 H34 N3 O8 P; Mol wt: 607.5966

ACTION – Potent protein tyrosine kinase Src SH2 domain ligand ($IC_{50} = 0.25$ nM) with high selectivity over Lck ($IC_{50} = 300$ nM). In an *in vitro* assay, compound significantly inhibited bone resorption (93 and 74% inhibition of rat pit formation at 25 and 2.5 μ M, respectively). Potentially useful for the treatment of osteoporosis. Other related compounds are:



Compound	R1	R2	R3	Formula
RU-85048 [293481]²	H	OPO3H2	2-thienyl	C ₂₈ H ₃₂ N ₃ O ₇ PS
RU-81843 [293482]^{1,2}	H	OPO3H2	Ph	C ₃₀ H ₃₄ N ₃ O ₇ P
RU-85052 [293830]^{1,2}	CO2H	CH(CO2H)2	Ph	C ₃₄ H ₃₅ N ₃ O ₉

SOURCE – Aventis Pharma.

REFERENCES

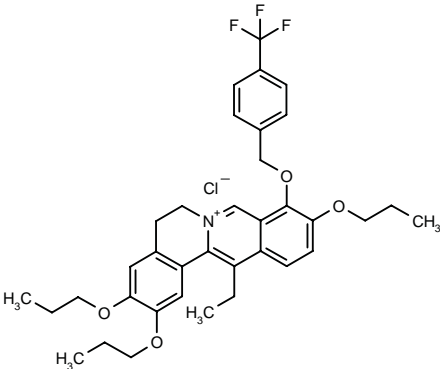
1. Deprez, P. et al. *Discovery of the malonate Src Sh2 binder RU85052. Synthesis and structure-activity studies*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst OC-13.

2. Deprez, P. et al. *SAR and rational design of Src SH2 binders around a heterocyclic scaffold identification of RU84687, a subnanomolar and Src SH2 selective binder*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-17.

TREATMENT OF LIPOPROTEIN DISORDERS

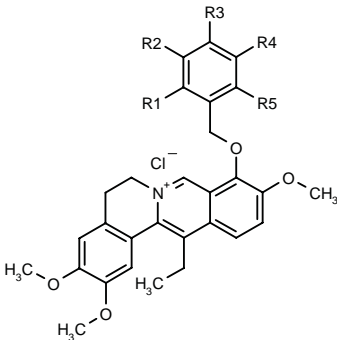
291755

13-Ethyl-2,3,10-tripropoxy-9-[4-(trifluoromethyl)benzoyloxy]-5,6-dihydrodibenzo[a,g]quinolizinium chloride



C36 H41 Cl F3 N O4; Mol wt: 644.1699

ACTION – Cholesterol biosynthesis inhibitor (IC₅₀ = 1 μM or less in human HepG2 cells) that acts by specifically inhibiting the enzyme sterol Δ¹⁴-reductase, which is involved in the distal pathway of cholesterol biosynthesis, thereby preventing the depletion of essential mevalonate derivatives. The compound decreased total cholesterol, LDL cholesterol and triglyceride levels by 33.1, 41.1 and 43.1%, respectively, at 0.3 mg/kg/day p.o. in hamsters. No signs of toxicity were observed in rats given oral doses over 2000 mg/kg and the LD₅₀ was determined to be > 3000 mg/kg. Other exemplified 5,6-dihydrodibenzo[a,g]-quinolizinium derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
291756	H	H	t-Bu	H	H	C ₃₃ H ₃₆ ClNO ₄
291757	F	F	F	F	F	C ₂₈ H ₂₅ ClF ₅ NO ₄
291758	H	H	CF3	H	H	C ₃₀ H ₂₉ ClF ₃ NO ₄

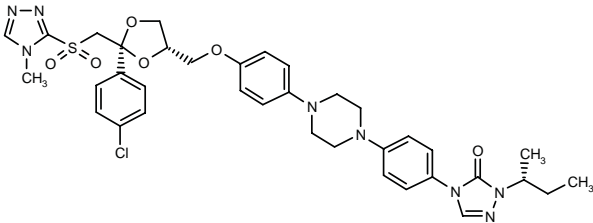
SOURCE – Hanwha.

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1. Kim, J.H. et al. (Hanwha Corp.) *Dibenzo[a,g]quinolizinium derivs. and the salts thereof*. JP 2000191662, WO 0037468.

291829

4-[4-[4-[4-[(2*S*,4*S*)-2-(4-Chlorophenyl)-2-(4-methyl-4*H*-1,2,4-triazol-3-ylsulfonylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl]piperazin-1-yl]phenyl]-2-[1 (*R*)-methylpropyl]-3,4-dihydro-2*H*-1,2,4-triazol-3-one



C36 H41 Cl N8 O6 S; Mol wt: 749.2889

ACTION – Lipid-lowering compound with an oxidized sulfur moiety that partially avoids the first-pass effect, thereby reducing the need to adjust the dose and frequency of administration for each subject to compensate for individual metabolism. The main mechanism of action of this compound appears to involve inhibition of microsomal triglyceride transfer protein (MTP), producing a decrease in LDL cholesterol and triglycerides. The compound exhibited IC₅₀ values of 61 nM for inhibition of apolipoprotein B (apoB) secretion in HepG2 cells and of 7.6 nM in an MTP inhibition assay.

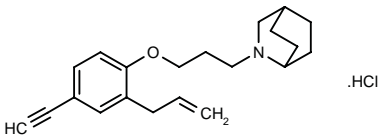
SOURCE – Janssen.

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1. Janssen, C.G.M. et al. (Janssen Pharmaceutica NV) *S-Oxide lipid lowering cpds*. WO 0037463.

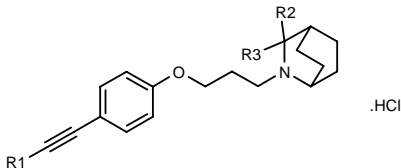
292435

2-[3-(2-Allyl-4-ethynylphenoxy)propyl]-2-azabicyclo-[2.2.2]octane hydrochloride



C21 H27 N O . HCl; Mol wt: 345.9112

ACTION – Cholesterol biosynthesis inhibitor that acts via inhibition of squalene synthase, with an IC₅₀ value for rat liver enzyme of 11 nM. The compound produced 50.4% inhibition of cholesterol biosynthesis at 30 mg/kg p.o. in rats. Other exemplified isoquinuclidine derivatives are:



Compound	R1	R2	R3	Formula
292436	H	H	H	C ₁₈ H ₂₃ NO.HCl
292437	5-quinolyl	-O-		C ₂₇ H ₂₆ N ₂ O ₂ .HCl
292438	4-(5-quinolyl)-Ph	-O-		C ₃₃ H ₃₀ N ₂ O ₂ .HCl

SOURCE – Kotobuki.

REFERENCES

1. Tomiyama, T. et al. (Kotobuki Pharmaceutical Co., Ltd.) *Isoquinuclidine derivs., their preparation method, and therapeutic agent for hypercholesterolemia containing them.* DE 19958246, GB 2344586, JP 2000169474.

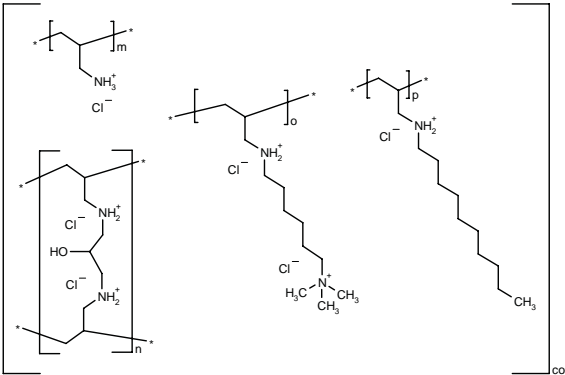
COLESEVELAM HYDROCHLORIDE⁺

Prop INN; USAN

222457

Allylamine polymer with 1-chloro-2,3-epoxypropane, [6-(allylamino)hexyl]trimethylammonium chloride and *N*-allyl-decylamine

GT31-104
GT31-104HB
CholestaGel (former tradename)



ACTION – Nonabsorbed lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption.

INDICATION – As an adjunct to diet and exercise for the reduction of elevated LDL cholesterol alone or in combination with an HMG-CoA reductase inhibitor, in patients with primary hypercholesterolemia when diet and exercise alone are not adequate.

PRESENTATION – Film-coated tablets, 625 mg; capsules, 375 mg.

PROPRIETARY NAME – Welchol (US).

SOURCES – GelTex; Sankyo Pharma.

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3. Mandeville, W.H. III and Holmes-Farley, S.R. (GelTex Pharmaceuticals, Inc.) *Method for removing bile salts from a patient with alkylated amine polymers.* US 5679717.

4. Mandeville, W.H. III and Holmes-Farley, S.R. (GelTex Pharmaceuticals, Inc.) *Alkylated amine polymers.* US 5693675.

5. Mandeville, W.H. III and Holmes-Farley, S.R. (GelTex Pharmaceuticals, Inc.) *Process for removing bile salts from a patient and alkylated composition therefor.* US 5917007.

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16. Rosenbaum, D.P. et al. *Absorption, distribution and excretion of CholestaGel(TM), a novel bile acid sequestant, in dogs in rats.* FASEB J 1996, 10(3): Abst 2637.

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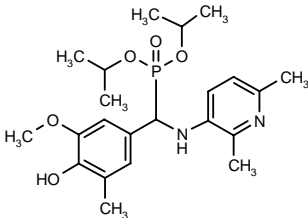
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⁺Drug Data Rep 1998, 020(04): 0366.

SR-74829i/SB-253149*

268702

1-(2,6-Dimethylpyridin-3-ylamino)-1-(4-hydroxy-3-methoxy-5-methylphenyl)methylphosphonic acid diisopropyl ester



C22 H33 N2 O5 P; Mol wt: 436.4857

ACTION – Hypolipidemic agent with lipoprotein(a) (Lp[a])-lowering activity. In primary cultures of cynomolgus monkey hepatocytes, compound reduced apolipoprotein(a), the key apoprotein of Lp(a), by 36% at 20 μ M. *In vivo* in cynomolgus monkeys, orally administered compound was found to reduce plasma levels of Lp(a), with lesser inhibition of cytochrome P-450.

SOURCES – SmithKline Beecham; Symphar.

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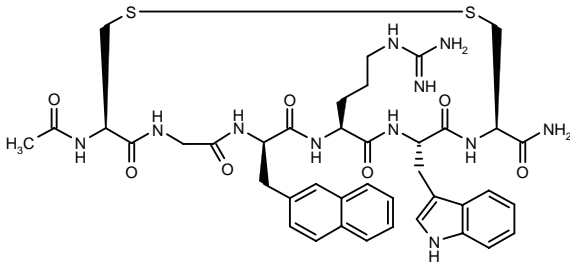
2. Nguyen, L.M. et al. *Synthesis of a new series of aminophosphonate compounds with lipoprotein(a) lowering activity.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-144.

*Identified compound **268702** Drug Data Rep 1998, 020(10): 0856.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

291716

N-Acetyl-L-cysteinyl-glycyl-3-(2-naphthyl)-D-alanyl-L-arginyl-L-tryptophyl-L-cysteinamide cyclic (1-6)-disulfide



C40 H49 N11 O7 S2; Mol wt: 860.0291

ACTION – A compound with high affinity for melanocortin receptor, particularly active at the MC₄ receptor. It caused a concentration-dependent inhibition of [¹²⁵I]-NDP-MSH binding to murine B16 melanoma cells with a K_i of 2.51 μ M versus respective K_i values for the human MC₁, MC₃, MC₄ and MC₅ receptors of 3543, 228, 12.4 and 5118 nM. When the compound was administered i.p. at 0.5 mg/kg to rats, food intake increased by 48% after 4 h compared to basal food intake. Significant and dose-dependent improvement in withdrawal behavior was observed in opioid-dependent rats. Specifically claimed for the treatment of eating and weight disorders, as well as for the therapy of inflammation and drug addiction.

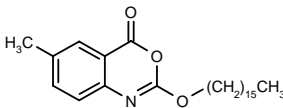
SOURCE – Melacure Therapeutics.

REFERENCES

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292439

2-(Hexadecyloxy)-6-methyl-4H-3,1-benzoxazin-4-one



C25 H39 N O3; Mol wt: 401.5871

ACTION – Selective lipase inhibitor shown to produce 98.7% inhibition of pancreatic lipase at 500 nM, while only 4 and 12.5% inhibition of trypsin and chymotrypsin activity, respectively, was observed at the same concentration. A representative compound from a series of benzoxazinones with potential in the treatment of obesity and obesity-related disorders.

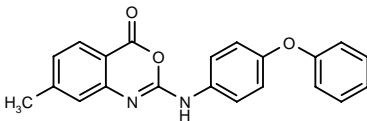
SOURCE – Alizyme.

REFERENCES

1. Hodson, H.F. et al. (Alizyme plc) *2-Oxy-4H-3,1-benzoxazin-4-ones for treatment of obesity.* WO 0040569.

292440

7-Methyl-2-(4-phenoxyphenylamino)-4H-3,1-benzoxazin-4-one



C21 H16 N2 O3; Mol wt: 344.3684

ACTION – A representative compound from a series of benzoxazinones with potential in the treatment of obesity and obesity-related disorders, found to inhibit human and porcine pancreatic lipase with respective IC₅₀ values of 1 and 2 μ M or less.

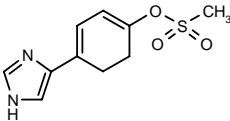
SOURCE – Alizyme.

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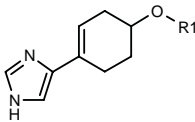
292640

Methanesulfonic acid 4-(4-imidazolyl)-1,3-cyclohexadien-1-yl ester

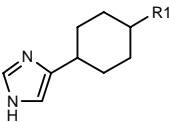


C10 H12 N2 O3 S; Mol wt: 240.2818

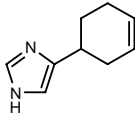
ACTION – Histamine H₃ receptor antagonist, potentially useful for the treatment of obesity and eating disorders, emesis, pain and neurogenic inflammation. Other exemplified substituted imidazole derivatives include the following:



Compound	R1	Formula
292641	H	C ₉ H ₁₂ N ₂ O
292642	4-Cl-PhNHCO	C ₁₆ H ₁₆ ClN ₃ O ₂



Compound	R1	Isomer	Formula
292643	4-Cl-PhNHCOO		C ₁₆ H ₁₈ ClN ₃ O ₂
292644	2,4-(Cl)2-PhCH2NHCOO	trans	C ₁₇ H ₁₉ Cl ₂ N ₃ O ₂
292645	OH	trans	C ₉ H ₁₄ N ₂ O
292646	4-CN-PhO	cis	C ₁₆ H ₁₇ N ₃ O
292647	4-CN-PhO	trans	C ₁₆ H ₁₇ N ₃ O
292648	(4-F-Ph)2CHO	trans	C ₂₂ H ₂₂ F ₂ N ₂ O
292649	3-CF3-PhO	cis	C ₁₆ H ₁₇ F ₃ N ₂ O



292651: C9 H12 N2

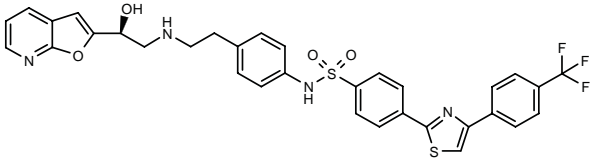
SOURCES – Boehringer Ingelheim; Novo Nordisk.

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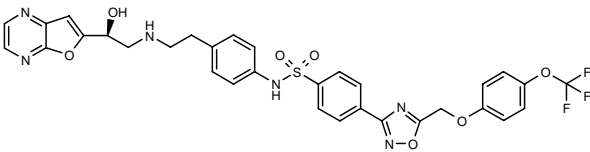
292678

N-[4-[2-[2(S)-(Furo[2,3-*b*]pyridin-2-yl)-2-hydroxyethyl-amino]ethyl]phenyl]-4-[4-[4-(trifluoromethyl)phenyl]-thiazol-2-yl]benzenesulfonamide



C33 H27 F3 N4 O4 S2; Mol wt: 664.7263

ACTION – Potent and selective β_3 -adrenoceptor agonist (EC₅₀ = 1.5 nM for stimulating increases in cAMP in CHO cells transfected with human receptors) with > 100-fold selectivity relative to β_1 - and β_2 -adrenoceptors (IC₅₀ = 310 and 170 nM, respectively, for inhibition of [¹²⁵I]-iodo-cyanopindolol binding). Potentially useful for the treatment of obesity. Another bicyclic heteroarylethanolamine-containing compound is:



292680: C32 H37 F3 N6 O7 S

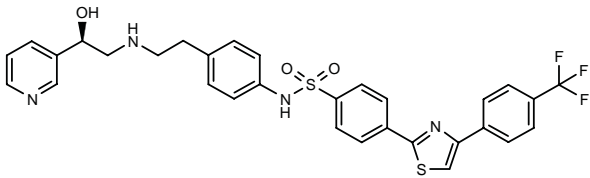
SOURCE – Merck & Co.

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292681

N-[4-[2-[2(R)-Hydroxy-2-(3-pyridyl)ethylamino]ethyl]-phenyl]-4-[4-[4-(trifluoromethyl)phenyl]thiazol-2-yl]benzenesulfonamide



C31 H27 F3 N4 O3 S2; Mol wt: 624.7053

ACTION – Potent and selective β_3 -adrenoceptor agonist (functional EC₅₀ = 3.6 nM; 94% activation; binding IC₅₀ = 46 nM) with markedly less activity at β_1 - (EC₅₀ = 4800 nM; IC₅₀ = 2300 nM) and β_2 -adrenoceptors (EC₅₀ = 2400 nM; IC₅₀ = 2300 nM). Compound also showed over 100-fold selectivity for β_3 -adrenoceptors over a panel of other receptors and ion channels, except for human dopamine D2 and D3 receptors (61- and 26-fold selectivity, respectively). Compound exhibited good oral bioavailability in both dogs and rats (38 and 17%, respectively) and a long duration of action. Selected for phase I clinical studies as a potential treatment for obesity.

SOURCE – Merck & Co.

REFERENCES

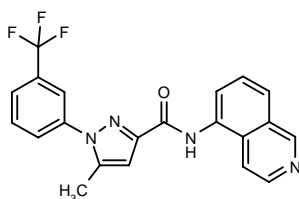
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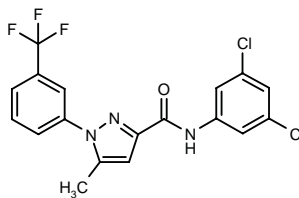
292689

N-(5-Isoquinolinyl)-5-methyl-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazole-3-carboxamide



C21 H15 F3 N4 O; Mol wt: 396.3705

ACTION – Potent and selective neuropeptide Y (NPY) Y_5 receptor antagonist (IC_{50} = 80 nM for inhibition of [^{125}I]-PYY binding in HEK293 cells transfected with the human Y_5 receptor) proven able to reduce food intake in a rat feeding model (38% at 2 h after 30 mg/kg p.o.). Potentially useful for the treatment of obesity. Another aminopyrazole Y_5 receptor antagonist is:



292688: C18 H12 Cl2 F3 N3 O

SOURCE – R.W. Johnson.

REFERENCES

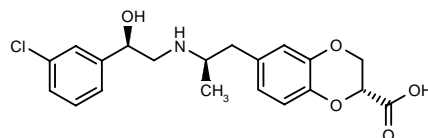
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2. Kordik, C.P. et al. *Pyrazole-based antagonists of the human neuropeptide- Y_5 (NPY5) receptor*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 304.

N-5984

292588

6-[2(*R*)-[2(*R*)-(3-Chlorophenyl)-2-hydroxyethylamino]-propyl]-2,3-dihydro-1,4-benzodioxine-2(*R*)-carboxylic acid



C20 H22 Cl N O5; Mol wt: 391.8488

ACTION – Potent and selective β_3 -adrenoceptor agonist with EC_{50} values of 4.5 and 910 nM, respectively, for stimulating cAMP production in CHO cells expressing human β_3 - and β_1 -adrenoceptors. It induced lipolysis in rat white adipocytes with an EC_{50} of 0.47 nM, versus values for relaxation of guinea pig trachea and stimulation of guinea pig right atrial frequency of 34.8 nM and 393 nM, respectively. Potentially useful for the treatment of obesity and type 2 diabetes.

SOURCE – Nisshin Flour Milling.

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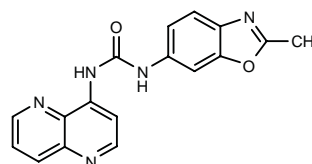
2. Ueno, M. et al. (Nisshin Flour Milling Co., Ltd.) *6-(2-(R)-Aminopropyl)-1,4-benzodioxane-2-(R)-carboxylate derivs. and their preparation method*. JP 1999140079.

3. Yanai, M. et al. *Novel β_3 adrenergic receptor agonists*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 303.

SB-334867

293484

N-(2-Methylbenzoxazol-6-yl)-*N'*-(1,5-naphthyridin-4-yl)urea



C17 H13 N5 O2; Mol wt: 319.3227

ACTION – Orexin-1 (OX-1) receptor antagonist (pK_b = 7.4) with excellent selectivity over OX-2 receptors (pK_b = 5.7) and 5-HT $_{2B}$ and 5-HT $_{2C}$ receptors (pK_i = 5.4 and < 5.3, respectively). In rats, compound showed good CNS penetration and was able to inhibit both spontaneous and orexin A-induced feeding at a dose of 30 mg/kg i.p., and to inhibit orexin A-induced grooming at a dose of 10 mg/kg i.p. Potentially useful for the treatment of obesity.

SOURCE – SmithKline Beecham.

REFERENCES

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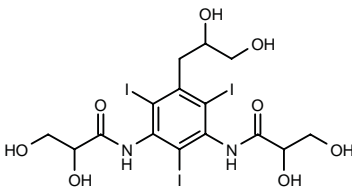
3. Arch, J.R.S. et al. *A selective orexin-1 receptor antagonist reduces food intake in male and female rats*. *Obes Res* 2000, 8(Suppl. 1) Abst: O162.

4. Rodgers, R.J. et al. SB334867, a novel orexin₁ receptor antagonist, enhances behavioural satiety & dose-dependently blocks orexin A-induced hyperphagia in rats. *J Psychopharmacol* 2000, 14(3, Suppl.): Abst PJ6.

DIAGNOSTIC AGENTS

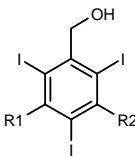
291787

N-[3-(2,3-Dihydroxypropionamido)-5-(2,3-dihydroxypropyl)-2,4,6-triiodophenyl]-2,3-dihydroxypropionamide



C15 H19 I3 N2 O8; Mol wt: 736.0211

ACTION – Low-viscosity iodinated contrast medium for X-ray imaging. The compound has good water solubility and acceptable viscosity and osmolality levels, while it demonstrates lower acute toxicity than previously known low-viscosity contrast agents. The maximum tolerated dose for this compound was 15.0-17.5 g of iodine/kg of body weight. Other specifically claimed iodinated aryl compounds are:



Compound	R1	R2	Formula
291788	NHCOCH(OH)-CH(OH)CH2OH	NHCOCH(OH)-CH(OH)CH2OH	C ₁₅ H ₁₉ I ₃ N ₂ O ₉
291789	CONHCH2-CH(OH)CH2OH	NHCOCH(OH)-CH(OH)CH2OH	C ₁₅ H ₁₉ I ₃ N ₂ O ₈
291790	N(COCH2OH)-CH2CH(OH)CH2OH	CONHCH2-CH(OH)CH2OH	C ₁₆ H ₂₁ I ₃ N ₂ O ₈
291791	N(COCH2OH)-CH2CH(OH)CH2OH	CONHCH(CH2OH)-CH(OH)CH2OH	C ₁₇ H ₂₃ I ₃ N ₂ O ₉

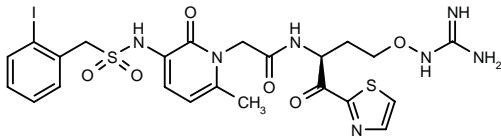
SOURCE – Nycomed Imaging.

REFERENCES

1. Andersson, S. et al. (Nycomed Imaging AS) *Water-soluble contrast media for X-ray imaging*. WO 0037115.

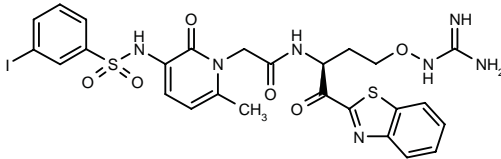
292685

N-[3-(Guanidinoxy)-1(*S*)-(thiazol-2-ylcarbonyl)propyl]-3-(2-iodobenzylsulfonamido)-6-methyl-2-oxo-1,2-dihydropyridine-1-acetamide



C23 H26 I N7 O6 S2; Mol wt: 687.5334

ACTION – Nonpeptide iodinated thrombin inhibitor (K_i = 14 nM against human enzyme) potentially useful as a diagnostic agent for imaging clots via visualization of clot-bound thrombin. Another compound within this series of iodinated heteroaryl ketones is:



292686: C26 H26 I N7 O6 S2

SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

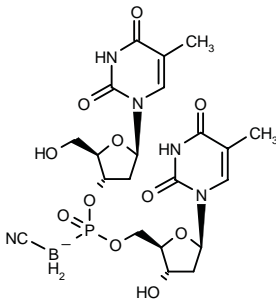
1. Pan, W. et al. *Heteroaryl keto thrombin inhibitors: Design and synthesis*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 285.

PHARMACOLOGICAL TOOLS

292727

Cyanoboraneidephosphonic acid thymidin-3'-*O*-yl, thymidin-5'-*O*-yl diester

Cyano[(thymidin-3'-*O*-yl)(thymidin-5'-*O*-yl)phosphoryl]-dihydridoborate(1-)



C21 H28 B N5 O11 P; Mol wt: 568.2612

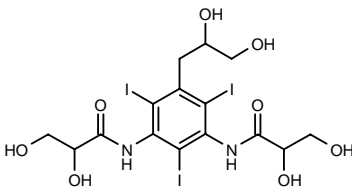
3. Arch, J.R.S. et al. *A selective orexin-1 receptor antagonist reduces food intake in male and female rats*. *Obes Res* 2000, 8(Suppl. 1) Abst: O162.

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DIAGNOSTIC AGENTS

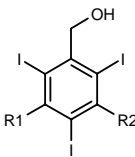
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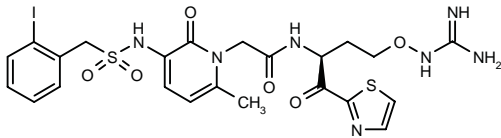
SOURCE – Nycomed Imaging.

REFERENCES

1. Andersson, S. et al. (Nycomed Imaging AS) *Water-soluble contrast media for X-ray imaging*. WO 0037115.

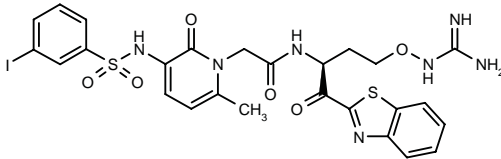
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292686: C26 H26 I N7 O6 S2

SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

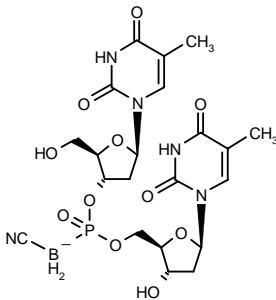
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PHARMACOLOGICAL TOOLS

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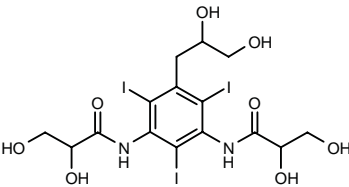
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DIAGNOSTIC AGENTS

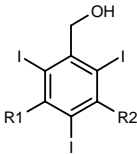
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291790	N(COCH2OH)-CH2CH(OH)CH2OH	CONHCH2-CH(OH)CH2OH	C ₁₆ H ₂₁ I ₃ N ₂ O ₈
291791	N(COCH2OH)-CH2CH(OH)CH2OH	CONHCH(CH2OH)-CH(OH)CH2OH	C ₁₇ H ₂₃ I ₃ N ₂ O ₉

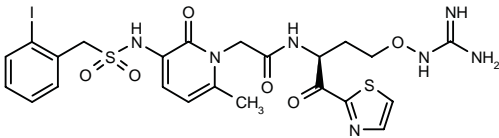
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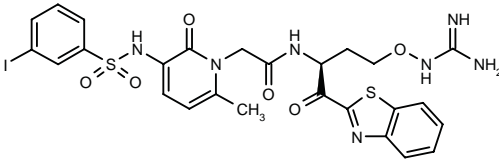
292685

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292686: C26 H26 I N7 O6 S2

SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

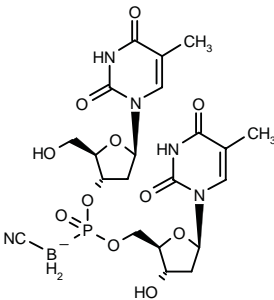
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PHARMACOLOGICAL TOOLS

292727

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Cyano[(thymidin-3'-*O*-yl)(thymidin-5'-*O*-yl)phosphoryl]-dihydridoborate(1-)



C21 H28 B N5 O11 P; Mol wt: 568.2612

ACTION – Dinucleoside cyanoboranophosphate compound that shows similarity to natural nucleic acids and unique properties such as high lipophilicity and resistance to enzymatic cleavage. It therefore represents a promising lead for designing a wholly new class of modified nucleotides and nucleic acids with utility for diagnostic and therapeutic applications including as carriers of ^{10}B in boron neutron capture therapy for the treatment of cancer.

SOURCE – Duke University, Durham, NC (US).

REFERENCES

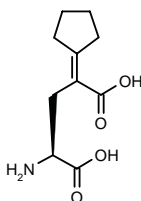
1. Lin, J.-L. and Shaw, B.R. *Novel nucleic acid mimic: Nucleoside P-cyanoboranophosphate*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 43.

LY-339624^{*,1,2}

269092

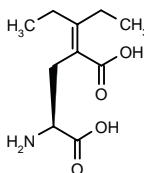
(2S)-2-Amino-4-cyclopentylideneglutaric acid

4-Cyclopentylidene-L-glutamic acid



C10 H15 N O4; Mol wt: 213.2315

ACTION – Potent ionotropic glutamate GluR5 ligand ($K_i = 32.6$ nM) with high selectivity ($K_i > 1\text{-}10$ μM) relative to other kainate receptor subtypes and AMPA receptors. Compound exhibited functional agonist activity *in vitro* in both rat dorsal root ganglion neurons ($\text{EC}_{50} = 1.05$ μM) and HEK293 cells expressing GluR5 receptors ($\text{EC}_{50} = 6.2$ μM). Potentially useful as a pharmacological tool for the investigation of the functional role of GluR5 receptors. Another glutamic acid derivative is:



LY-339687 [292949]²: C10 H17 N O4

SOURCES – Lilly; NPS Allelix.

REFERENCES

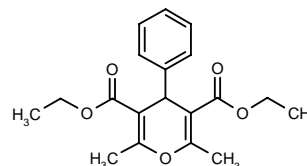
1. Pedregal Tercero, C. and Rubio Esteban, A. (Lilly SA) *Glutamic acid derivs. and pharmaceutical compns. for the treatment of central nervous system disorders*. EP 0867430, ES 2133095, JP 1998279542.
2. Baker, S.R. et al. *4-Alkylidenyl glutamic acids, potent and selective GluR5 agonists*. Bioorg Med Chem Lett 2000, 10(16): 1807.

^{*}Identified compound **269092** (see **269083**) Drug Data Rep 1998, 020(11): 0933.

MRS-1704^{*}

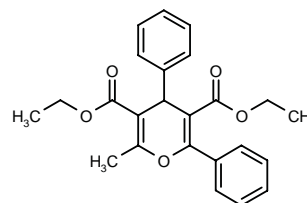
248098

2,6-Dimethyl-4-phenyl-4H-pyran-3,5-dicarboxylic acid diethyl ester



C19 H22 O5; Mol wt: 330.3840

ACTION – Adenosine A_3 receptor antagonist ($K_i = 381$ nM for binding to human A_3 receptors) with 57-fold selectivity over rat A_1 receptors ($K_i = 21.9$ μM) and inactive against A_{2A} receptors. Another specifically claimed substituted 4H-pyran derivative is:



MRS-1705 [292541]: C24 H24 O5

SOURCE – Bayer.

REFERENCES

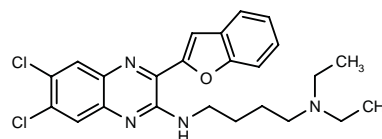
1. Urbahns, K. et al. (Bayer AG) *Subst. 4H-pyrans with a modulating effect on potassium channels*. CA 2183048, DE 19529858, EP 0758648, JP 1997059271, US 5760073.
2. Jacobson, K.A. et al. *Pyran template approach to the design of G protein-coupled receptor antagonists*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 263.
3. Li, A.H. et al. *Pyran template approach to the design of novel A3 adenosine receptor antagonists*. Drug Dev Res 1999, 48(4): 171.

^{*}Identified compound **248098** Drug Data Rep 1997, 019(06): 0501.

PD-0210293^{2,3}

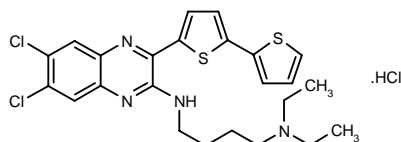
292463

*N*¹-[3-(1-Benzofuran-2-yl)-6,7-dichloroquinoxalin-2-yl]-*N*⁴,*N*⁴-diethylbutane-1,4-diamine



C24 H26 Cl2 N4 O; Mol wt: 457.4024

ACTION – Nonpeptide IL-8 (CXCR1/CXCR2) receptor antagonist with an IC_{50} value of 0.2 μ M in a neutrophil chemotaxis assay and of 0.09 μ M for antagonism of IL-8 binding to its receptor. Compound also shows affinity for certain other 7-membrane G-protein-coupled receptors including M_2 , NK_2 and 5-HT_{1A} receptors (IC_{50} = 0.53, 0.15 and 0.97 μ M, respectively). Potentially useful as a tool to elucidate the role of IL-8 in inflammatory diseases. Another 2-amino-3-heteroarylquinoxaline is:



PD-0220245 [280348]*^{1,2}: C₂₄ H₂₆ Cl₂ N₄ S₂ . HCl

SOURCE – Pfizer.

REFERENCES

1. Carson, K.G. et al. (Warner-Lambert Co.) *Substd. quinoxaline derivs. as interleukin-8 receptor antagonists*. WO 9942461, WO 9942463.
2. Li, J.J. et al. *Structure-activity relationship of 2-amino-3-heteroaryl-quinoxalines as potent, non-peptide interleukine-8-receptor antagonists*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 144.
3. Trivedi, B.K. *Chemokines: Targets for novel therapeutics*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 324.

*Identified compound **280348** Drug Data Rep 1999, 021(10): 0904.
